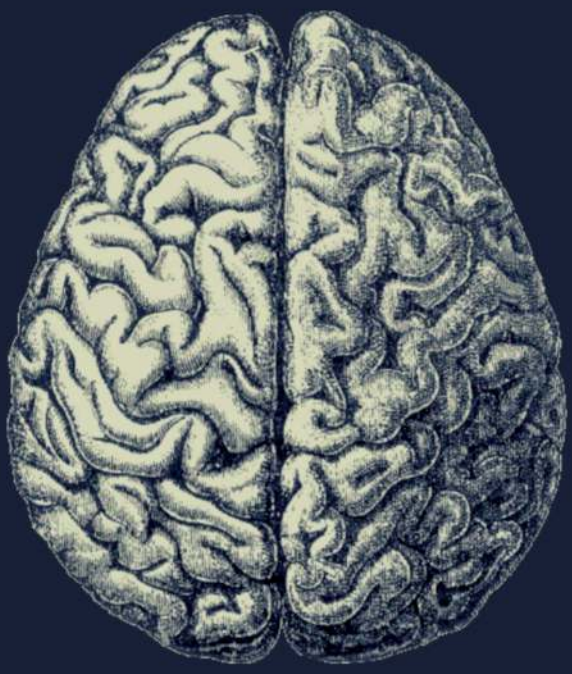
AWAKE BRAIN SURGERY IN GLIOBLASTOMA PATIENTS

Jasper K.W. Gerritsen



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Colofon

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CHAPTER 1

Aim of the thesis

Glioblastoma (grade IV astrocytoma) is the most common primary brain malignancy in adults. The current standard therapy consists of tumor resection followed by adjuvant chemotherapy and radiotherapy. This regimen leads to a median overall survival of 16 months [1-3]. The most important goal of surgery is to resect as much of the tumor as safely possible, which can be measured as extent of resection or residual tumor volume. This matters, since a higher extent of resection and a lower residual tumor volume have been associated with improved survival outcomes [4-14]. Notably, due to the invasive nature of glioblastoma, total resection of the tumor ("gross-total resection") is technically impossible but the semantic use of the concept remains [4]. Previous studies have shown that gross-total resection especially leads to superior survival outcomes [4-14]. However, many glioblastomas are located in or near eloquent areas, which can deem pursuing gross-total resection while preventing neurological deficits rather challenging. In order to push the boundaries of the resection safely, the surgeon can decide to use "mapping" techniques. With mapping techniques, the surgeon is able to "map", or locate the eloquent areas of the brain: the areas of the brain with a specific, clear function that can be tested during the operation. Examples of these areas are the motor areas (responsible for the movement of arms and legs), language areas (responsible for the production and adequate understanding of language), sensory areas (responsible for tactile or painful stimulation of bodily surfaces) and visual areas (responsible for processing retinal information in order to create a coherent image of the outside world). One of the most frequently used mapping techniques is an awake craniotomy (also called: awake brain mapping). At the start of an awake craniotomy, the patient is sedated while the surgeon opens the skull (trepanation). During the actual tumor resection, the patient is awake and is subjected to a series of tasks. Common examples are counting, object picture naming, repeating words, and opening and closing of the hand. While the patient executes these tasks, the surgeon stimulates the area around the tumor with currents that are initiated by a small handheld stimulator or with strip electrodes [14,15]. Since stimulation of healthy brain tissue inhibits normal brain function at that particular location, it gives the surgeon information about the potential histology of the tissue (tumor vs. healthy brain) and the eloquence of the tissue (eloquent vs. "silent") that is subject to stimulation. Consequently, after repeated stimulation of a range of locations, the surgeon is able to delineate tumor from healthy brain tissue and locate eloquent areas which need to be preserved during tumor resection. This information allows the surgeon to make informed decisions about which parts of the tumor to resect and which not, and to what extent the resection can be performed safely.

Until recently, awake brain mapping was most commonly used during resections of low-grade gliomas (grade II astrocytomas or grade II oligodendrogliomas). In these patients, it showed great potential and was associated with less postoperative neurological deficits and an increased extent of resection – which corresponded well with the rationale behind

this technique [16-21]. Low-grade glioma patients on average have a significantly longer median survival than high-grade glioma patients (including glioblastoma). Taking into consideration the relatively young age of the typical low-grade glioma patient and his or her prognosis of multiple years, improving survival outcomes and preserving neurological function during these years was of utmost importance in these patients. Indeed, the increased extent of resection as a result of awake brain mapping was associated with improved survival times in these patients.

Traditionally, glioblastoma cases were approached much more defensively than low-grade glioma tumors, since damaging these patient's neurological functioning – which would severely impair the quality of life of these patients – was considered unethical when taking into consideration their rather dim prognosis. Since a large part of the neurosurgical community felt that safeguarding neurological performance was more important than risking the patient's functioning in order to resect the last few percent of tumor tissue, eloquent glioblastoma surgery often consisted of tumor debulking or tissue biopsy. For many, it was simply "not worth taking the risk". Since postoperative chemotherapy and radiotherapy are strong prognostic factors for survival in these patients, this approach ensured that the patient's chances for receiving adjuvant therapy – and indirectly, his or her survival – would not be impaired by the resection.

Recently, however, it has been shown that awake brain mapping can be a useful tool in glioblastoma resections as well. In 2008, Sanai *et al* published a well-known study in which they investigated the use of awake mapping in glioblastoma patients with language-eloquent tumors [14]. They found that it enabled the surgeon to increase the extent of the resection significantly, and more importantly, in a safe manner. In 2011, Sacko *et al* directly compared awake craniotomy with asleep resection for supratentorial tumors, including glioblastomas as well [22]. They found that awake mapping led to less neurological complications and higher extents of resection. In 2012, de Witt Hamer *et al* summarized the evidence of mapping techniques in glioma patients and reported outcomes that confirmed the results of previous studies [23]. Various papers about the role of awake brain mapping in glioblastoma surgery were published, but they included other supratentorial tumors as well in their analysis or based their analyses on fairly limited, single-center patient cohorts, rendering the level of evidence of the technique's use in glioblastoma patients specifically rather suboptimal [17,18,24-27].

The presented thesis will aim to address key questions regarding the use, benefit and indication setting of awake brain mapping in glioblastoma patients. Ideally, studying its effect in these patients should be done using five "pillars", which could be employed simultaneously:

(1) A quantitative summary of the literature (meta-analysis) to condense the available evidence and to identify major scientific hiatuses which need to be addressed in subsequent studies.

(2) A pilot retrospective cohort study to directly compare awake mapping with asleep mapping in glioblastoma patients for various key outcomes: postoperative neurological deterioration, postoperative worsening of quality of life, extent of resection, residual tumor volume, and survival outcomes. This study should be adequately designed and powered to identify potential differences in these primary outcomes.

(3) A large-scale multicenter retrospective cohort study in order to generate sufficient power to carry out subgroup analyses, since it would not be sufficient to study the impact of awake mapping only in glioblastoma patients as a whole. This project should be focused on patients with eloquent tumors, since these concern the resections during which the dilemma of maximizing extent of resection/preventing neurological deficits is the most pronounced. Additional analyses should be done to evaluate the use, benefit and indication setting of this technique in clinically relevant subgroups, stratifying patients for important predictive factors such as age, preoperative neurological functioning and preoperative KPS. This would enable the surgeon to improve his or her decision making with regard to surgical planning in individual patients.

(4) An international multicenter prospective cohort study to validate the results of the retrospective studies in a prospective setting. Questions regarding the indication setting, impact on specific outcomes, and the effect of different mapping procedures can be answered with adequate power. Ideally, this project should be embedded in a Consortium of institutes which would allow new insights to be addressed in subsequent spin-off studies.

(5) A randomized controlled trial to assess the value of awake mapping in glioblastoma patients with the highest level of evidence possible in a prospective setting. Randomization will minimize the risk of selection bias and confounding which have both the potential to be highly present in studies investigating awake mapping. A RCT that is well designed and carried out will be able to generate the ultimate evidence in terms of quality.

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CHAPTER 2

General introduction

Safe surgery for glioblastoma: Recent advances and modern challenges

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ABSTRACT

One of the major challenges during glioblastoma surgery is balancing between maximizing extent of resection and preventing neurological deficits. Several surgical techniques and adjuncts have been developed to help identify eloquent areas both preoperatively (fMRI, nTMS, MEG, DTI) and intraoperatively (imaging (ultrasound, iMRI), electrostimulation (mapping), cerebral perfusion measurements (fUS)), and visualization (5-ALA, fluorescein)). In this review, we give an update of the state-of-the-art management of both primary and recurrent glioblastomas. We will review the latest surgical advances, challenges and approaches that define the onco-neurosurgical practice in a contemporary setting and give an overview of the current prospective scientific efforts.

INTRODUCTION

Glioblastoma (grade IV astrocytoma) is the most common form of primary brain malignancy in adults. Patients face a dim prognosis of approximately 16 months, which has not significantly improved over the last 15 years[1]. Standard therapy includes resection followed by adjuvant chemoradiation, which can be administered in various ways dependent on the patient's age and performance (Stupp protocol, Perry protocol)[2,3].

One of the most important factors in determining the patient's prognosis is surgery (the extent of resection)[4-6]. First, glioblastoma patients who have undergone tumor resection experience on average a longer overall survival than those who have undergone tissue biopsy[6]. Second, the extent of resection (EOR) in surgery plays a major role, since higher EOR percentages correlate with better survival outcomes[4,5].

Due to their invasive nature, glioblastomas infiltrate the surrounding parenchyma and despite a gross-total resection, recurrence is inevitable. Still, neurosurgeons aim to safely resect as much tumor tissue as possible, often striving for complete resection of the contrast-enhancing (CE) part of the tumor on MR-imaging, adhering to the fact that complete resection of the contrast-enhancing tumor has shown to convey a survival benefit[7]. Recent evidence suggests that it might be beneficial to expand the resection to the non-contrast-enhancing (NCE) part as well in two distinct subgroups of patients: (1) patients with *IDH* wildtype tumors, regardless of MGMT methylation status and (2) in younger patients, regardless of *IDH* status[8].

Since >50% of glioblastomas are located in or near eloquent areas, aggressive resection has the potential to lead to postoperative neurological deficits, thereby severely harming the patient's quality of life (QoL) and functioning[4-6]. In order to preserve the patient's quality of life (and protect neurological functioning) while maximizing the extent of resection, several preoperative and intraoperative methods have been developed to help the surgeon balance between these two - sometimes conflicting - goals. The postoperative functioning is of utmost importance, since suboptimal postoperative QoL or KPS negatively impact survival chances of glioblastoma patients[9].

In this review, we will briefly elaborate on the standard of care for both primary and recurrent glioblastoma. We will describe the recent advances in the surgical management of glioblastoma patients and the current challenges neurosurgeons are facing. We will discuss both grade 4 astrocytoma and glioblastoma, according to the 2021 WHO classification (formerly known as *IDH*mt and *IDH*wt glioblastoma in the 2016 WHO classification). Various surgical techniques will be discussed as well as the use of intraoperative imaging and

surgical adjuncts. At last, we will provide an overview of the studies that have recently been completed, are currently active, or are prospectively planned. Non-surgical adjuncts for glioma resections such as LITT (laser interstitial thermal therapy), OCT (optical coherence tomography), mass spectrometry, and tumor treating fields (TTF) are outside the scope of this paper.

Contemporary management of glioblastoma

Glioblastomas can be divided in primary, secondary, and recurrent glioblastomas. Standard of care for primary glioblastoma consists of maximal safe resection followed by adjuvant chemoradiotherapy[2,3]. Extent of resection (EOR), expressed as the percentage of tumor resected or postoperative residual tumor volume, has shown to be a prognostic factor[4-6]. Generally, a distinction can be made between subtotal (STR) versus near-total (NTR) versus gross-total resections (GTR), but there is no consensus of standard, validated cut-off values for STR, NTR and GTR for neither extent of resection or residual tumor volume. Other well-known prognostics include age, preoperative patient functioning (Karnofsky Performance Scale, KPS), and molecular status (MGMT and IDH)[2,11-14].

With very rare exceptions, these tumors regrow and no explicit standard-of-care exists at recurrence. Viable treatment options include, but are not restricted to: re-resection, re-irradiation, re-challenge TMZ, second-line chemotherapy (Lomustine), or experimental study treatments, dependent on the patient's clinical performance[15].

Previous randomized controlled trials with second-line drug regimens including i.a. anti-VEGF (Bevacizumab, Cediranib)[16-18], anti-TGFβ-receptor-I (Galunisertib)[19], TKI-inhibitor (Axitinib)[20], anti-receptor tyrosine kinase (RTK) (Regorafenib)[21], anti-protein kinase C (PKC) (Enzastaurin)[22] and anti-EGFR (Depatux-M)[23] failed to show significant outcome improvements.

Brain mapping

A substantial portion of glioblastomas is located in or near eloquent areas, which can affect the patient's neurological functioning. Eloquent brain areas include the bilateral frontal motor areas (cortical structures such as the primary motor cortex, premotor cortex and the supplementary motor cortex, and subcortical structures such as the corticospinal tract, arcuate fasciculus, inferior fronto-occipital fasciculus and internal capsule), the bilateral parietal somatosensory areas (postcentral gyrus), the bilateral primary visual cortex in the occipital lobes, and the speech areas of Broca and Wernicke in respectively the left frontal and temporal lobes[24].

Resection of tumors in these areas proves to be challenging, since the exact location of eloquent areas differs between patients. Furthermore, delineation of glioblastoma is often difficult due to their invasiveness. An accurate and reliable method to differentiate eloquent brain areas from both non-eloquent areas and tumor tissue is therefore necessary. Since extent of resection is important for the patient's survival, maximizing the percentage of tumor resected (minimizing the residual tumor volume) is one of the most important goals of glioblastoma surgery. For this purpose, brain mapping is one of the most commonly used methods. Brain mapping can be performed both preoperatively (nTMS, MEG, DTI, fMRI) and intraoperatively (awake mapping or asleep mapping). Motor and somatosensory mapping can be performed both awake and asleep, while speech function (Broca's area and Wernicke's area) can only be tested while the patient is awake.

Preoperative brain mapping

Four modalities are mainly used for the preoperative brain mapping in glioma and glioblastoma resections: nTMS (navigated transcranial magnetic stimulation), MEG (magnetoencephalography), fMRI (functional MRI) and DTI (diffusion tract imaging).

nTMS stimulates the brain with transcranial magnetic pulses, thereby creating a cortical electrical field which leads to neuronal stimulation or inhibition. The obtained results are then paired with the neuronavigation system, in order to combine the information regarding functional areas with the raw MRI images for intraoperative assessment. Neuronal stimulation can be achieved by a single magnetic pulse, while a repetitive pulse causes inhibition of the cortical area. nTMS is most frequently used for motor mapping[25], but retrospective evidence regarding its use for language mapping is reported as well[26,27]. To reduce TMS-noise in TMS-based language mapping, automated speech algorithms have been built for which proof of concept has been established[28]. A major factor of concern is the correlation between functional areas identified preoperatively by nTMS and the respective identification of these areas by direct electrostimulation intraoperatively. A recent meta-analysis by Jeltema *et al* demonstrates that the average correlation between these two modalities is between 2 and 16 mm[29], but most articles found <10 mm achievable. Moreover, they found that the validity of nTMS for language mapping varied greatly when compared with DES: sensitivity differed between 10 and 100%, specificity from 13.3-98%, negative-predictive value from 57 and 100% and positive predictive value between 17 and 75%[29].

The group in Munich has done extensive work on the use of nTMS in glioma surgery[27,30-32]. In a retrospective 2015 paper, they found that, in comparison with the non-nTMS group, nTMS was associated with a smaller size of the craniotomy, less residual tumor tissue, shorter length-of-stay, increased proportion of patients receiving adjuvant therapy and improved survival at 3, 6 and 9 months in glioblastoma patients. No significant difference was found

for surgery-induced neurological deficits[27]. In contrast, Frey *et al* found in in a prospective cohort of 250 glioma patients significant less postoperative deficits in the nTMS group than in the control group (8.5% vs. 6.1%) as well as a higher proportion of gross-total resections (59% vs. 42%)[33]. In 2013, Picht *et al* prospectively compared nTMS with DES during awake craniotomy in 20 patients with language-eloquent gliomas in a collaborative study of the Berlin and the Munich groups[34]. They reported a sensitivity and negative predictive value of 100% for Broca's area for nTMS, even though its reliability and specificity in Wernicke's area proved to be rather limited. Moreover, they found that on a total of 10 glioblastoma patients, 6 patients maintained their preoperative speech functionality, 3 patients had an improvement and the aphasia of 1 patient was permanently worsened at 3 months postoperatively. For motor-eloquent gliomas, the Leuven group retrospectively developed a realistic electric field-based model of nTMS outperforming the point-cloud models in term of prediction of motor responses intraoperatively[35].

Thus, nTMS can be used for mapping of primary motor areas during motor-eloquent glioblastoma resections. Though, due to uncertainties of nTMS and possible intra-operative confounding factors (such as brain shift), real-time intraoperative monitoring control is warranted for maximal safety. In language-eloquent gliomas, nTMS is mainly used for the preoperative surgical planning and should be mainly used as an adjunct next to conventional DES to map and resect these tumors adequately.

We searched the United States National Library of Medicine and National Institute of Health Trial Register (clinicaltrials.gov), the EU Clinical Trials Register, the Netherlands Trial Register (NTR) and the ISRCTN register for recently completed trials (between 1 January 2018 and 1 November 2020), currently active trials and planned trials evaluating the surgical management for primary or recurrent glioma. We found that the use of nTMS in motor-eloquent gliomas is currently evaluated by the Munich group in a quadruple-blinded RCT including 330 patients, comparing nTMS-guided resections with conventional resections with postoperative neurological deficits at 3 months as primary outcome (still accruing without current results, Table 1).

MEG (magnetoencephalography) is a comparatively new mapping tool, which detects magnetic fields that are elicited by neuronal electrical currents in order to delineate functional from non-functional brain areas. MEG identifies functional areas before the operation based on task-based activity, similar to fMRI. Zimmerman *et al* retrospectively compared MEG with fMRI for localization of functional perirolandic areas in 13 patients with gliomas, AVMs and hemangiomas[36]. They found a solid congruency between both modalities with an average spatial distance of 10 mm. In a 2012 paper, Tarapore *et al* retrospectively compared MEG and nTMS with intraoperative DES in 24 glioma patients[37]. They reported that the

average distance between the nTMS and DES motor-eloquent sites was 2.1 mm and between nTMS and MEG 4.7 mm. nTMS was deemed reliable for negative mapping: no motor sites that were identified as negative by nTMS were found positive for motor function during intraoperative DES. Of the 7 glioblastoma patients included, only 1 patient experienced a minor postoperative deficit of the right arm (MRC grade 4 paresis).

More recently, Traut *et al* reported on the use of MEG for evaluating neuroplasticity and language organization after glioma surgery[38]. They concluded that functional reorganization is present in most glioma patients postoperatively, more so in patients who had undergone resection of tumors in the language-dominant hemisphere.

One of the major drawbacks of MEG is the cost of the necessary equipment and the need for a dedicated setting with adequate expertise. Consequently, this modality is still scarcely used despite its potential in clinical practice.

DTI (diffusion tract imaging) is used for white-matter fiber tracking based on diffusion-weighted imaging (DWI) MRI sequences. Four tracts are commonly visualized by DTI: the corticospinal tract (CST), arcuate fasciculus (AF), optic radiation (OR) and inferior fronto-occipital fasciculus (IFOF). DTI is based on the anisotropy (diffusion varies with direction) of water molecules, thereby deriving the precise direction of the axons within every voxel. The white matter tracts can be derived from the magnetic gradients of all voxels combined, indicating the orientation of single fibers. FA (fractional anisotropy) is the most frequently used method to measure these gradients. When these measurements are combined with anatomical ROIs (regions-of-interest), a 3D map of the four tracts mentioned above can be incorporated in weighted MR-images to visualize the specific, individual trajectory in which the color represents the orientation of the most dominant eigenvector of that particular voxel. It therefore supplies information regarding displacement, disruption and infiltration of the white matter with the concurrent presence or absence of edema. Therefore, DTI is often used in glioblastoma patients as a tool for preoperative surgical planning[39], outcome prediction[40,41] and intraoperative decision making[42,43].

Sensitivity and specificity of DTI in comparison with DES are >90% but it suffers from important limitations[44]. Since there is no standard protocol for DTI (e.g., selecting ROIs and fiber tracking), external generalizability, precision and accuracy can be adversely affected. Furthermore, it is susceptible to challenges that are common to preoperatively conducted imaging such as unreliable spatial congruency due to brain shift. Last, an important inherent limitation of DTI is commonly described as the "crossing fiber problem", for which DTI has a very limited visualization accuracy.-Advanced DTI techniques such as HARDI q-ball imaging have been tested. Although they are effective in identifying language tracts preop-

eratively and in predicting functional outcome postoperatively, they generally suffer from the same limitations as standard DTI[45]. New techniques such as CSD (constrained spherical deconvolution), DKI (diffusional kurtosis imaging) and DSI (diffusion spectrum imaging) show promising results and are potentially more adept at improving reproducibility and intraoperative accuracy[46-48].

Two British studies are currently investigating the use of DTI in glioma patients in the PRaM-GBM study (Cambridge) and the FUTURE-GBM study (Oxford) (Table 1).

fMRI (functional MRI) identifies eloquent areas based on task paradigms and consequently increased levels of blood oxygen in the respective functional areas as a surrogate for increased neuronal activity. BOLD (blood oxygen level-dependent) MRI sequences are used as contrast images. The correlation between fMRI-identified eloquent areas is high with Wada testing but not always with direct electrostimulation, with considerable variances being found in different retrospective and review studies[49,50]. Moreover, fMRI has been shown to suffer from suboptimal specificity caused by neurovascular uncoupling. This can occur due to disruption of regular white matter perfusion as caused by intraparenchymal tumors[51-53]. fMRI-based detection of eloquent areas can therefore only be used as a surgical adjunct and remains heavily reliable on confirmation by intraoperative methods. As of now, the Beijing Neurosurgical Institute and the M.D. Anderson Cancer Center are prospectively evaluating the use of fMRI in glioma patients (Table 1).

Intraoperative brain mapping: awake and asleep

Motor mapping can be performed when the patient is awake (awake craniotomy under local anesthesia) or asleep (general anesthesia). Cortical stimulation of the motor areas can be performed-with two methods: direct electrostimulation (DES) with a handheld probe or the usage of a subdural grid with strip (grid) electrodes (adjacent to the central sulcus)[54,55]. DES in its turn can be performed with the low-frequency technique, in which a stimulator with a 50-Hz (Europe) or 60-Hz (USA, Canada) frequency is used for functional localization, or with the high-frequency technique (train-of-five stimulation)[54,56]. Both the low-frequency technique and the high-frequency technique can be carried out safely with a monopolar or bipolar stimulation device. The stimulation intensity of the device ranges between 1 and 20 mA with increasing steps of 0.5-1.0 mA. Subcortical motor mapping can be achieved by DES with a handheld probe with similar or slightly adjusted stimulation settings. Gogos *et al* recently reported on their prospective study evaluating "triple motor mapping" (transcranial, bipolar and monopolar), in which they found that monopolar high-frequency stimulation was more effective at identification of subcortical motor pathways (86.4% of cases) than bipolar stimulation (10.2% of cases)[57].

The identification of motor-eloquent areas under awake circumstances differs from mapping when the patient is asleep. During awake mapping, motor function is assessed by the involuntary movement (positive response) or impaired motor function (negative response) of muscles in the face, arm or leg. In contrast, during asleep mapping, MEPs (motor-evoked potentials) are used to assess the integrity of cortical motor structures and its descending subcortical tracts[58]. Evoked potentials are recorded with the use of EMG needle electrodes in the contralateral extremity. Generally, reduction of the amplitude of the evoked potentials of more than 50% or the necessity to increase the stimulation current significantly represent clinically significant changes. Amplitude reductions can be reversible, which generally are a sign of temporary motor deficits, and irreversible, rather suggesting new motor deficits[59,60].

Speech mapping can be performed only when the patient is awake. Cortical stimulation near speech areas is performed most commonly with the use of a bipolar stimulator with the electrodes 0.5 cm apart. The surgeon usually starts with a low stimulus between 1.0 and 2.0 mA and maps the cortex for 2 seconds every 0.5-1.0 cm. Positive or negative stimulation sites are noted and eloquent areas are avoided. Frequently used tests for language function include the Boston naming test, Token test, semantic associations, counting, verb generation and word fluency[60]. The surgeon maps the surface various times with increasing currents. Subcortical stimulation of language-associated fibers can be performed similarly[54,60].

One of the most promising new awake mapping techniques includes functional ultrasound (fUS). fUS uses Doppler ultrasound images to detect changes in brain tissue perfusion while the patient carries out certain motor or linguistic tasks, allowing the surgeon to identify eloquent areas based on a vascular, rather than a mechanical basis. Advantages of fUS include its high spatiotemporal resolution, wide field of view, high depth penetration and its low-cost of implementation. Imbault *et al* described this technique in 2017 as a proof-of-principle, using fUS to successfully identify eloquent areas in all 28 low-grade glioma patients[61]. In 2020, the Rotterdam group published their experience with using fUS during awake surgery in 10 low-grade and high-grade glioma patients. They demonstrated with this prospective study that fUS can be used to map both motor and language function accurately[62].

New developments in asleep mapping techniques led to the progression towards continuous monitoring of the motor structures' integrity with a technique called continuous dynamic mapping (CDM). This technique utilizes a monopolar probe at the tip of the suction device and has been pioneered by the team from Bern. Thanks to the known current-distance relationship of monopolar stimulation, the surgeon can resect tumor tissue close to motor pathways with stepwise decreasing stimulation intensity while continuously being guided by the different sounds of the device (indicating the distance to the motor fibers)[63]. Subcortical mapping is performed using a monopolar with the train-of-five technique with a 0.5

ms pulse duration, an interval of 4 ms and an intensity ranging from 1 to 20 mA. Recently, they published their update on the CDM technique in 182 patients with intra-axial tumors within 1 cm of the CST[64]. Six of those patients (3%) had a permanent motor decrease of 0.5 points or more on the MRC scale: half of them were due to ischemic injury, half of them were due to mechanic injury (1.7%)[64]. CDM can therefore be deemed as a very safe, feasible and intuitive alternative for conventional asleep mapping methods in order to prevent neurological deficits after motor-eloquent glioma surgery.

The benefit of brain mapping in glioma surgery has been demonstrated by various groups. Sanai *et al* published in 2008 a large well-known study investigating 245 patients undergoing awake craniotomy (AC) for speech-eloquent gliomas[54]. They found that the use of AC permits the surgeon to maximize extent of resection while minimizing language deficits: the incidence of permanent language deficits after 6 months was 1.6% with a mean extent of resection of 69.0% among glioblastoma patients. In 2011, Sacko *et al* prospectively compared awake craniotomy with surgery under general anesthesia for resections of supratentorial lesions in a prospective setting[65]. They included 575 patients with gliomas, metastases, cavernous malformations and meningiomas, and found that patients who had undergone awake craniotomy had better postoperative neurological outcomes and increased extent of resection rates. They observed permanent postoperative neurological deficits in 4.6% of patients operated with awake craniotomy and in 16% of patients operated under general anesthesia. De Witt Hamer *et al* published their landmark paper in 2012, evaluating the impact of intraoperative stimulation mapping (ISM) in a meta-analysis including 90 papers covering a total of 8,091 patients[66]. They found that resections with mapping led to fewer late severe neurologic deficits (3.4% vs. 8.2%) and were simultaneously more extensive (GTR in 75% vs 58%). These results were in line with the meta-analysis of Gerritsen *et al* published in 2018 which evaluated the impact of mapping techniques in high-grade glioma specifically[67]. They found that ISM-led resections were associated with improved overall survival (16.9 months in the ISM group vs. 12.0 months in the GA group), less postoperative complications (13% vs. 21%) and a higher incidence of GTR (79% vs 48%).

Awake mapping has several limitations. First, reliable mapping information often can be obtained only when patients have near-intact or intact function of language or motor-based tasks. Function impairments can hamper the reliability of the procedure which can harm the accuracy and precision of the mapping. Second, awake craniotomies are known to have the potential to cause after-discharges (ADs – stimulation-induced epileptic discharges) and stimulation-evoked seizures[68]. ADs can be recorded with EEG or ECoG and are electroencephalographic alterations after electrostimulation that are similar to seizures or can progress into them[69]. Intraoperative seizures can be managed by applying ice-cold saline to the exposed brain surface, administration of anti-epileptic drugs (AEDs), benzodiazepines,

propofol, or even by terminating the mapping procedure and continuing the resection under general anesthesia[70,71]. However, intraoperative stimulation-evoked seizures tend to not occur if the current is low (i.e., 2-2.5 mA). Third, extreme obesity could interfere with a safe airway surveillance and is therefore an important anesthesiological contraindication for awake craniotomies. Last, false positive findings during intraoperative stimulation can occur due to mental fatigue of patients during long procedures which may challenge the interpretation of the patient's performance and the identification of eloquent areas, consequently.

There is no general consensus regarding mapping techniques and procedures. A 2014 survey evaluating stimulation mapping techniques in epilepsy surgery found a wide range of local paradigms [72]. Though, the inconsistencies between centers and countries in glioma mapping are virtually unknown at this moment. For example, the choice between awake mapping and asleep mapping is largely based on the surgeon's expertise, as is the preference for DES versus subdural grid electrodes, bipolar versus monopolar probe, the current's range and increasing steps, the assessment of motor and speech function during awake craniotomy (neurophysiologist/neuro-linguist vs. trained assessor vs. patient himself/herself), the use of ECoG or intraoperative EEG to detect epileptic activity intraoperatively, the use of additional surgical adjuncts during mapping procedures such as 5-ALA, DTI, ioMRI and ultrasound; and the anesthesia technique during awake craniotomy (awake-awake-awake versus asleep-awake-asleep or asleep-awake-awake) for example. Moreover, one of the most challenging parts of mapping techniques during glioma surgery is the decision-making process, i.e., on which information the decision to alter the surgical strategy or to end the resection is based. For many surgeons, this decision frequently is based on the combination of multiple concurrent information sources: the patient's task performance (during awake craniotomy), the evoked potentials' amplitude (during asleep mapping), the imaging (neuronavigation with or without DTI) and the macroscopy (expertise and fluorescence). To gain understanding in the local techniques and procedures that are used for glioma resections in different centers and countries, the ENCRAM Consortium has carried out two international surveys evaluating this inter-center variability in mapping procedures and decision making[73,74]. Together with large, well-designed prospective studies, the results from this survey may be the first step towards reaching a general consensus regarding the use of these techniques in glioblastoma patients.

Currently, three prospective clinical studies are currently evaluating the use of intraoperative mapping techniques in glioma patients: two randomized controlled trials (RCT): a large one in the Netherlands and Belgium (SAFE trial, 246 patients) and a smaller one at the Mayo clinic (50 patients); and one prospective cohort study from the transatlantic ENCRAM Consortium (PROGRAM study) (Table 1)[75].

Intraoperative fluorescence and imaging

Three main tools are used during surgery to increase the extent of resection and minimize residual tumor volume: fluorescence (including 5- aminolevulinic acid (5-ALA) and fluorescein), ultrasound, and intraoperative MRI (ioMRI).

The use of 5-ALA (Gliolan®), a precursor of haemoglobin, results in the accumulation of fluorescent porphyrin IX in cells lacking ferrochelatase (e.g. glioblastoma cells) and is therefore used to visualize tumor cells *in vivo* with the use of an adjusted neurosurgical microscope. Another fluorescence agent, (sodium) fluoresceine, designed to be an intravascular fluorophore, passes the (dysfunctional) blood-brain barrier in glioma patients, as opposed to the intratumoral synthesis of 5-ALA.

Fluorescence is mainly used to increase extent of resection in glioma surgery. However, the ultimate goal is maximizing EOR while minimizing postoperative deficits. Stummer *et al,* found that GTR was confirmed in 65% of the patients in the 5-ALA group which was a significantly higher proportion than in the white light group (36%)[76]. Moreover, the 5-ALA group had a higher progression-free survival at 6 months postoperatively (41% vs. 21%). Although their study was not powered for overall survival, they found that the 5-ALA group had a non-significant shorter OS than the white-light group (13.5 months vs. 15.2 months, p=0.1). Notably, in 2011 a supplemental analysis was published which showed that patients in the 5-ALA group had more early postoperative neurological deficits[77]. Forty-eight hours after surgery, the proportion of patients with NIHSS (National Institute of Health Stroke Scale) deterioration of 1 point of more in the 5-ALA group was 26.2% versus 14.5% of patients in the white light group. After 6 weeks, this was decreased to 17.1% in the 5-ALA group and 11.3% in the white light group (p=0.29) and 3 months postoperatively, the difference was negligible between groups (19.6% in the 5-ALA group and 18.6% in the white light group, p=0.77). KPS deterioration did not differ significantly between groups during follow-up. They concluded that a postoperative transient deficit weighs up against the long-term benefits of using 5-ALA (longer PFS, higher chance of GTR)[76,77]. Since then, various studies have demonstrated the benefit of 5-ALA among different subgroups of brain tumor patients[78-80]. However, the differentiation between tumorous and healthy tissue in the marginal area of the tumor remains a common challenge during 5-ALA guided resections[81]. Since the levels of fluorescence are much lower in this area, the delineation between different tissues is obscured which makes 5-ALA guided resections somewhat subjective to the surgeon's expertise. Objective quantification remains therefore moderately limited. Another major limitation of 5-ALA is the lack of guidance in the resection of the non-contrast-enhancing part of the tumor, which has recently been shown to be of utmost importance in glioma surgery. Molinaro *et al* from the UCSF group demonstrated in a large retrospective

cohort of 761 patients that maximum resection of the non-contrast-enhancing part of the tumor leads to increased overall survival, regardless of their IDH-status[8].

A recent study by Hansen *et al* retrospectively compared the use of 5-ALA with fluorescein during high-grade glioma resections[82], which showed no difference regarding mean extent of resection (96.9% in the 5-ALA group, 97.4% in the fluorescein group), the proportion of patients with GTR (defined as residual tumor volume of $<0.175m^3$; 29.5% in the 5-ALA group and 36.2% in the fluorescein group), median overall survival (14.8 months in the 5-ALA group and 19.7 months in the fluorescein group) or median progression free survival (8.7 months in the 5-ALA group and 9.2 months in the fluorescein group).

Two prospective studies have investigated the use of yellow fluorescein in high-grade glioma patients. Falco *et al* reported on their preliminary results of the FLUOCERTUM study, in which they found a 74.2% rate of GTR in their high-grade glioma subgroup of 128 patients[83]. Acerbi *et al* found in their FLUOGLIO study that GTR was achieved in 82.6% of their HGG patients (n=57)[84]. Moreover, 6-months PFS was 56.6%, 12-months PFS was 15.2% and median overall survival was 12 months.

Recently, Schipmann *et al* reported on the combined use of 5-ALA and photodynamic therapy (PDT) in a prospective cohort study in recurrent high-grade glioma patients[85]. The accumulated porphyrins caused by 5-ALA are both fluorescence agents and photosensitizers, which in combination with PDT leads to cellular damage by reactive oxygen species (ROS). They included 20 patients in their series in which they achieved GTR in 45% of patients, median PFS of 6 months (95% CI 4.8-7.2) and no adverse events, deeming this novel application of 5-ALA a safe and promising tool for recurrent glioma surgery. Therefore, the team from Münster (Germany) has planned a randomized controlled trial including 106 patients in which biopsy will be compared with biopsy + PDT with 5-ALA for recurrent glioblastoma patients with PFS as primary outcome (Table 1).

Intraoperative ultrasound (ioUS) is the use of sonography to locate tumor tissue during surgery and to delineate it from healthy brain tissue. Similar to 5-ALA, ioUS is one of the tools to potentially increase the extent of resection. However, ioUS is able to identify both low-grade and high-grade glioma (as opposed to 5-ALA, which can only identify high-grade glioma). Theoretically, 5-ALA and ioUS can be considered complementary techniques since the former visualizes tumor tissue macroscopically and the latter is able to detect nodular remnants that might get hidden behind collapsing cavity walls after large tumor resections. One of the main advantages of ioUS over preoperative imaging modalities is the possibility to visualize the tumor in real-time (with taking into account brain shift), which is especially useful for subcortical lesions. Moreover, its corresponding costs (and duration to acquire

images) are much lower than other intraoperative imaging methods, such as intraoperative MRI (ioMRI; the cost of which is a well-known limitation), with a significantly lower spatial resolution than ioMRI as a consequence.

There is an increasing amount of research interest in using ioUS in glioma surgery, in particular retrospective evidence in low-grade glioma patients. In 2015, Petridis *et al* evaluated the use of ioUS in low-grade glioma surgery[86]. They found that it was well-suited for identification of tumor tissue and major blood vessels. Gerganov *et al* compared ioUS with ioMRI for resections of low-grade gliomas and concluded that both modalities are well-suited to locate the tumor and its borders before resection starts[87]. However, based on their results the quality of ioMRI proves to be superior to ioUS during the resection, and is better suited to detect residual tumor, particularly because the difference in spatial resolution and the subsequent interpretation of the images. ioUS proved to be prone to problems in differentiating artifacts such as blood clots and fluids from true residual tumor tissue, which has been reported before[88]. Though, other studies found ioUS to be accurate in identifying tumor tissue after glioma resection and assessing extent of resection[89,90]. Coburger *et al* suggested a comparable sensitivity and specificity of ioMRI to ioUS, deeming ioUS ideal for centers lacking a ioMRI[91]. Trevisi *et al* recently published a large meta-analysis regarding the use of ioUS in glioma patients including 13 studies[92]. They demonstrated that the pooled sensitivity of ioUS in detecting residual tumor tissue was 72.2% and the specificity was 93.5%. Detection was complicated by artifacts, small volume of residual tumor (<5 ml) and previous radiotherapy[90].

Scientific evidence for the use of ioUS in high-grade glioma is rarer. Incekara *et al* published the results of their single-center randomized controlled trial in 2021[93]. They included 50 glioblastoma patients and randomized them with a 1:1 ratio between resection with or without the use of ioUS. They found that gross-total resection was achieved more often in the ioUS group (8 of 23 vs. 2 of 24, $p = 0.036$) without increased rates of postoperative neurological deficits. Furthermore, there is evidence that ioUS can be used to detect residual tumor and therefore could increase extent of resection in high-grade glioma, equal to ioMRI[94]. This is supported by the study of Solheim *et al,* in which they used ioUS in a series of 156 high-grade glioma patients. They found that medium or good ultrasound image quality was independently associated with a higher incidence of gross-total resection[95].

Wang *et al* prospectively compared 137 patients undergoing glioma resection with the help of ioUS with a control group of 60 patients[96]. They found that the 1-year and 2-year survival in for both low-grade and high-grade glioma patients was longer in the ioUS group than in the control group. Recently, Liang *et al* and Prada *et al* have reported on their use of contrast-enhanced ultrasound (CEUS) in high-grade glioma patients with improved dif-

ferentiation between artifacts and residual tumor tissue[97-99]. Colleagues from Norway are working on improving the spatial resolution of ioUS by developing a new fluid (as compared to the conventional Ringer's lactate) to decrease image noise[100]. Another development is the integration of ioUS with neuronavigation (navigated intraoperative ultrasound; nUS) with subsequent 3D image acquisition (n3DUS)[101]. nUS has been shown to be able to detect residual tumor volume more reliably than conventional ultrasound[102].

The use of ioUS in glioma surgery is promising but is currently subject to contradictory results, since studies are mostly retrospective, small and heterogenous in study population. Currently, two prospective studies are evaluating its use for this patient group: he US-GLIOMA trial (results are expected soon) and the FUTURE-GBM study (recently started) (Table 1).

ioMRI is used to assess tumor extent of resection intraoperatively with the highest spatial resolution currently possible. Senft *et al* published their RCT evaluating the use of ioMRI in glioma surgery in 2011, including 58 patients[103]. They found that tumor resections in the ioMRI arm proved more often GTR than in the control group (96% versus 68%) with no difference in postoperative neurological complications. Furthermore, no patients in the ioMRI with GTR experienced postoperative neurological deterioration. Whiting *et al* reported on their retrospective series regarding the combined use of minimal access craniotomy with ioMRI and awake mapping in grade I-IV gliomas[104]. They found a median EOR of 98.5%, with GTR being achieved in 60.7% of LGG cases and in 30.3% of HGG casesMore than twenty-seven percent of the total group achieved an increase in EOR of more than 15% due to the use of ioMRI. A recent paper by Pichierri *et al* retrospectively compared the combined use of ioMRI and awake mapping with ioMRI in asleep patients and a (third) control group[105]. They found that the addition of ioMRI led to increased GTR rates among resections of all glioma grades, but there were no significant differences in EOR, tumor recurrences or overall survival between the awake ioMRI and asleep ioMRI group, although the three groups were biased for patient selection.

Recent evidence suggests that ioMRI might play a major role in enabling supratotal resection (i.e. resection of the tumor beyond the contrast-enhancing (CE) part into the surrounding non-contrast enhancing (NCE) part, but with radiological abnormalities on T2/FLAIR images). Two retrospective studies evaluated the association between ioMRI and supratotal resection. Li *et al* demonstrated that resection 53% of the NCE part led to additional survival benefit[106], whereas Pessina *et al* found that 45% would already lead to a significant improvement in survival outcomes[107]. Furthermore, Eyüpoglu *et al* showed in a prospective cohort series that the addition of ioMRI to resections with 5-ALA increased the NCE extent of resection, which was directly correlated to overall survival[108].

Major limitations of ioMRI are its high costs of installation and maintenance and the increased duration of the operation. Moreover, the use of ioMRI during eloquent gliomas is ideally combined with intraoperative mapping such as awake craniotomy or asleep mapping to test for tissue functionality and preserve speech and motor tracts.

Prospective evidence is needed to provide Level I evidence for the use of ioMRI. Currently, two prospective studies are conducted at the University Hospital Tübingen (Germany) and University Hospital Fudan (China) (Still accruing without current results, Table 1).

Intraoperative tissue sampling

Currently there are a few emerging techniques for intraoperative tissue sampling as an alternative to fluorescence. Vibrational spectroscopy is one of the most notable new techniques, with Raman spectroscopy (RS, based on inelastic scattering of photons) and Fourier-Transform Infrared spectroscopy (FTIS, based on the interaction of infrared radiation with tissue) as the two main modalities. RS and FTIS provide in a noninvasive manner real-time information about the molecular buildup of specific tissues. Consequently, they can potentially be used intraoperatively to assist the surgeon in distinguishing healthy brain parenchyma from tumor tissue. Recent evidence indeed suggests that spectroscopy can be used (1) to delineate the tumor margin, (2) to discern between specific histological tumor areas (e.g. tumor core, necrosis, infiltrative zone), (3) to evaluate the molecular tumor buildup (e.g. *IDH* status) and (4) to identify molecular tumor heterogeneity on both fresh tissue, frozen tissue and formalin-fixed paraffin-embedded (FFPE) brain tissue samples[109-112]. However, the use of these techniques is still in its experimental phase: studies focusing on *in vivo* validation, the interplay with intraoperative fluorescence and imaging and the added benefit when employed simultaneously with intraoperative mapping techniques are awaited.

Supratotal resection

Recently there has been growing interest in evaluating the benefit of "supratotal resection" (also called "supramarginal" or "supramaximal" resection, abbreviated: SpTR). The term "supratotal" applies to the extent of resection of the tumor outside the borders of the contrast-enhancing part of the tumor (as evaluated on T1+Gd images), i.e., the non-contrast-enhancing part (as evaluated on T2/FLAIR images). It can therefore be defined as GTR plus resection of some non-contrast-enhancement, as concluded by a recent crowdsourced consensus[113]. 2019, colleagues De Leeuw and Vogelbaum evaluated the use of supratotal resection in glioma in a systematic review[114]. They concluded that the available evidence was insufficient for "carte blanche" application and stressed the importance of validation in prospective cohort studies. In 2020, Molinaro *et al* published their well-known multicenter, retrospective cohort study, including 716 patients from UCSF, the Mayo Clinic and the Cleveland Clinic[8]. They found a significant association between supratotal resection and

longer overall survival in younger patients, regardless of *IDH* status, as well as in patients with *IDH*wt tumors regardless of MGMT status. Therefore, they proposed that in younger patients (<65 years old), maximal resection of the contrast-enhancing part should be pursued; and when safely feasible, the non-contrast-enhancing part as well (regardless of molecular status). Based on their dataset, maximal resection of the non-contrast-enhancing part was not recommended for patients aged >65 years. A smaller retrospective study by Hirono *et al,* which included 30 glioblastoma patients, also found that supratotal resection led to improved survival outcomes and was not associated with increased postoperative neurological deficits[115]. The results of these retrospective studies will be validated in the ENCRAM Consortium's prospective PROGRAM study[75].

Conclusions and future directions

Glioma surgery means balancing between maximizing extent of resection and preventing postoperative neurological complications. Various surgical techniques and adjuncts can be used, either to detect (residual) tumor tissue and to increase EOR (decrease residual volume) or to identify eloquent brain areas to preserve functionality. In recent years, a sizable amount of progress has been made for both goals by numerous scientific efforts. Neurosurgeons can choose from a wide array of possibilities their preoperative and intraoperative modality of choice. Different modalities can be used for the same goal, often with comparable outcomes or without strong, prospective evidence for one modality in particular. For some of these modalities and patient subgroups, the clinical impact is not always based on high-level evidence. Therefore, sizable prospective studies such as RCTs or multicenter cohort studies are needed to compare various modalities in a multimodal setting to determine which modality is best suited for which patient (grade, location, etc.). We gave an overview of current evidence for different surgical modalities and adjuncts for glioma surgery. Furthermore, we elaborated on the current prospective scientific efforts which will define the neurosurgical practice and decision making in the near future.

Table 1: Current prospective surgical studies in glioma patients

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
General									
RESURGE: Randomized Controlled Comparative Phase II Trial on Surgery for Glioblastoma Recurrence	NCT02394626	Randomized controlled trial, open label, parallel, 120 patients	Recurrent GBM	Resection followed by adjuvant second-line therapy	Adjuvant second-line therapy	Overall survival	Inselspital Bern (SUI)	Active, recruiting	1 May 2015-1 Oct 2021
Supramarginal Resection in Patients With Glioblastoma: A Randomized Controlled Trial	NCT04243005	Randomized controlled trial, double-blinded, parallel, 90 patients	GBM	Supramarginal resection with >10mm margin on T2 MRI	Conventional resection	Overall survival	St. Olav's University Hospital Trondheim (NOR)	Active, recruiting	1 Jul 2020-1 Mar 2027
Assessing Impact of Surgically-induced Deficits on Patient Functioning and Quality of Life (SIND Study)	NCT04007185	Prospective cohort study, 150 patients	High-grade glioma	Maximum safe resection	Biopsy	Impact of new deficit on quality of life (EORTC QLQ-30 and BN20)	Cambridge University Hospitals NHS Foundation Trust (UK)	Not yet recruiting	1 Feb 2020-1 Dec 2024 (Estimated)
Intraoperative mapping									
The SAFE-trial: Safe Surgery for Glioblastoma Multiforme: Awake Craniotomy versus Surgery Under General Anesthesia. A Multicenter Prospective Randomized Study	NCT03861299	Randomized controlled trial, open label, parallel, 246 patients	Primary, eloquent GBM	Awake craniotomy	Resection under general anesthesia	Proportion of gross-total resections, postoperative neurological morbidity	Erasmus MC Rotterdam (NL)	Active, recruiting	1 Apr 2019-1 Apr 2024

Table 1: Current prospective surgical studies in glioma patients (continued)

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
Awake vs. Asleep Craniotomy for Non-eloquent Gliomas	NCT03621748	Randomized controlled trial, single-blinded, parallel, 50 patients	Primary, non-eloquent glioma	Awake craniotomy	Resection under general anesthesia	Extent of resection	Mayo Clinic Jacksonville (FL, USA)	Active, recruiting	1 Jun 2020-1 Dec 2022
The PROGRAM-study: Awake mapping versus asleep mapping versus no mapping for glioblastoma resections	NCT04708171	Prospective cohort study, open label, parallel, 453 patients	High-grade glioma	Awake or asleep mapping	Conventional resection	Extent of resection, postoperartive neurological morbidity	Erasmus MC Rotterdam (NL)	Not yet recruiting	1 Feb 2021-1 Feb 2026 (Estimated)
Preoperative mapping									
The Application of ZOOMit-fMRI to Identify Motor Functional Cortex	NCT03091270	Prospective case-crossover study, 60 patients	Motor-eloquent gliomas	ZOOMit-fMRI-guided resection	BOLD-fMRI-guided resection	Accuracy of motor cortex localization	Beijing Neurosurgical Institute (CHN)	Active, recruiting	1 Feb 2016-1 Jan 2025
nTMS for Motor Mapping of Rolandic Lesions	NCT02879682	Randomized controlled trial, quadruple-blinded, parallel, 330 patients	Motor-eloquent gliomas	nTMS-guided resection	Conventional resection	Postoperative neurological deficits at 3 months	Technical University Munich (GER)	Active, recruiting	1 Aug 2016-1 Feb 2022
Safety and Feasibility of Preoperative and Intraoperative Image-Guided Resection of Gliomas	NCT03542409	Non-randomized clinical trial, open label, parallel, 40 patients	Primary glioma	Preoperative and intraoperative 2HG spectroscopy	Preoperative and intraoperative MR perfusion	Intraoperative imaging completion, postoperative complications	University of Utah (UT, USA)	Active, recruiting	6 Feb 2017-6 Feb 2023

Table 1: Current prospective surgical studies in glioma patients (continued)

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
Predicting Sites of Tumour Progression in the Invasive Margin of Glioblastomas (PRaM-GBM Study)	NCT03294434	Prospective cohort study, 120 patients	High-grade glioma	Resection with DTI	NA	Site of GBM true progression correctly predicted by DTI	Cambridge University Hospitals NHS Foundation Trust (UK)	Active, recruiting	2 Mar 2017-30 Sep 2021
Resting-State Functional MRI in Glioma Patients Before and After Surgery	NCT03964909	Single-arm clinical trial, open label, 30 patients	Speech-eloquent primary glioma	fMRI, CVR MRI or rs-fMRI	NA	Detectability of language networks	M.D. Anderson Cancer Center (TX, USA)	Active, recruiting	24 Apr 2017-12 May 2022
Intraoperative fluorescence and imaging									
5-Aminolevulinic Acid (5-ALA) to Enhance Visualization of Malignant Tumor	NCT02632370	Prospective cohort study, 69 patients	Primary or recurrent glioma	5-ALA guided resection	NA	Incidence of diagnostic tissue presence	Mount Sinai (NY, USA)	Completed	1 May 2016-31 Dec 2018
Intraoperative Ultrasound guided Glioma Surgery: a Randomized, Controlled Trial (US-GLIOMA)	NCT03531333	Randomized controlled trial, single-blinded, parallel, 50 patients	Primary high-grade glioma	Resection with intraoperative ultrasound	Resection without intraoperative ultrasound	Proportion of patients with gross-total resection	Erasmus MC Rotterdam (NL)	Completed	1 Nov 2016-1 Aug-2020
Interest of Fluorescein in Fluorescence-guided Resection of Gliomas (FLEGME study).	NCT03291977	Randomized controlled trial, open label, parallel, 62 patients	GBM	Resection with fluorescein	Conventional resection	Proportion of gross-total resections	Rennes University Hospital (FRA)	Active, recruiting	5 Oct 2017-1 Oct 2021
Quantification of ALA-induced PpIX Fluorescence During Brain Tumors Resection	NCT02191488	Single-arm non-randomized clinical trial, open label, 540 patients	Primary or recurrent glioma	5-ALA guided resection	NA	Intraoperative PpIX measurements vs coregistered histopathology	Dartmouth-Hitchcock Medical Center (NH, USA)	Active, not recruiting	1 Jul 2014-1 Jul 2021 (Estimated)

Table 1: Current prospective surgical studies in glioma patients (continued)

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
Diagnostic Performance of Fluorescein as an Intraoperative Brain Tumor Biomarker	NCT02691923	Randomized controlled trial, open label, parallel, 30 patients	Primary glioma	Fluorescein+5-ALA guided resection	Fluorescein-guided resection	Fluorescein performance	Dartmouth-Hitchcock Medical Center (NH, USA)	Active, not recruiting	1 Mar 2016-1 Dec 2021 (Estimated)
Improving Fluorescence-guided Brain Tumour Surgery With Ultra-high Sensitivity Imaging	NCT04556929	Single-arm clinical trial, open label, 20 patients	Primary glioma	5-ALA guided resection, biopsies from resection cavity	NA	Level of tumor fluorescence in images of resection cavity captured during surgery	Oxford University Hospitals NHS Foundation Trust (UK)	Not yet recruiting	1 Oct 2020-1 Aug 2022 (Estimated)
Stereotactical Photodynamic Therapy With 5-aminolevulinic Acid (Gliolan) in Recurrent Glioblastoma	NCT04469699	Randomized controlled trial, open label, parallel, 106 patients	Recurrent GBM	Biopsy followed by photodynamic therapy (PDT) with 5-ALA	Biopsy	Progression-free survival	University Hospital Münster (GER)	Not yet recruiting	1 Nov 2020-1 Nov 2025 (Estimated)
Impact of iMRI on the Extent of Resection in Patients with Newly Diagnosed Glioblastomas	NCT02379572	Non-randomized clinical trial, single-blinded, parallel, 315 patients	Primary GBM	Resection with iMRI guidance	Resection with 5-ALA guidance	Proportion of gross-total resections	University Hospital Tübingen (GER)	Active, recruiting	1 Jun 2015-1 Jun 2021
FUTURE-GB study: Functional and ultrasound-guided resection of glioblastoma	ISRCTN38834571	Randomized controlled trial, open label, parallel, 357 patients	Primary GBM	5-ALA, DTI, and US guided resection	5-ALA guided resection	Quality of life, overall survival, progression-free survival	Oxford University Hospitals NHS Foundation Trust (UK)	Active, recruiting	1 Apr 2020-30 Nov 2025

Table 1: Current prospective surgical studies in glioma patients (continued)

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
3.0T High-field Intraoperative MRI Guided Extent of Resection in Cerebral Glioma Surgery: a Single Center Prospective Randomized Triple-blind Controlled Clinical Trial	NCT01479686	Randomized controlled trial, triple-blinded, parallel, 321 patients	Primary glioma	3.0T iMRI-guided resection	Conventional neuronavigation-guided resection	Extent of resection	Fudan University Shanghai (CHN)	Active, not recruiting	1 Sept 2011-1 July 2021 (Estimated)

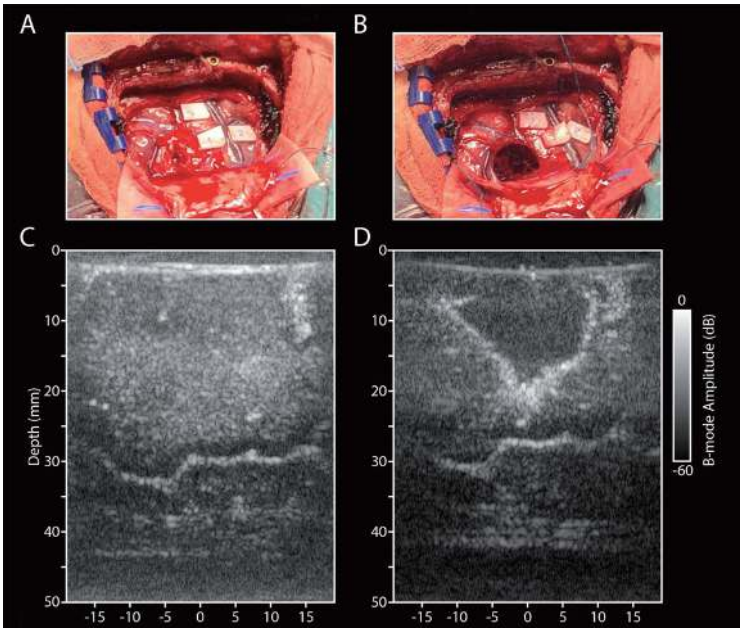

Figure 1: Intraoperative ultrasound. A: Intraoperative image of a glioma in the right parietal lobe. B: Intraoperative image of the cavity after tumor resection. C: Pre-resection B-mode image of the tumor and surrounding tissue. D: Post-resection B-mode ultrasound image of the resection cavity.

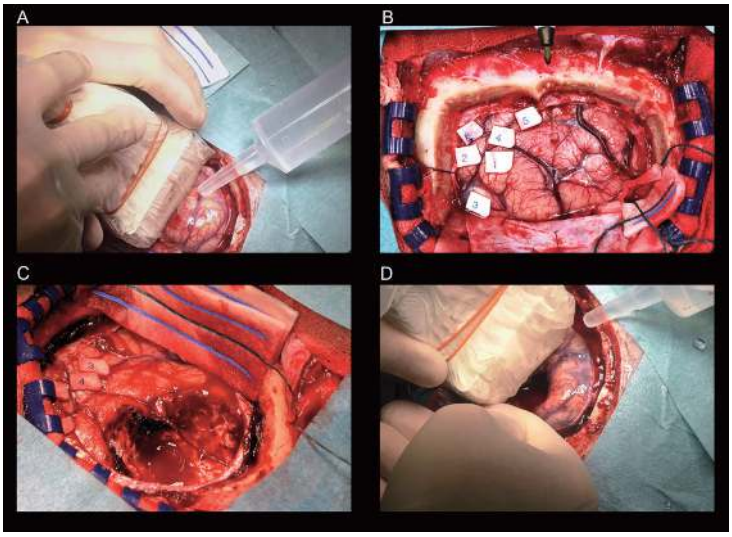

Figure 2: Electrocortical stimulation with intraoperative ultrasound. A: Intraoperative ultrasound before starting tumor removal. B: Electrocortical stimulation mapping using awake craniotomy to determine eloquent brain areas. C: Tumor resection based on mapping procedure, aided by the neuro-linguist. D: Intraoperative ultrasound after tumor resection to identify potential residual tumor.

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CHAPTER 3

Impact of intraoperative stimulation mapping on high-grade glioma surgery outcome: A meta-analysis

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ABSTRACT

Background

Intraoperative stimulation mapping (ISM) using electrocortical mapping (awake craniotomy, AC) or evoked potentials has become a solid option for the resection of supratentorial low-grade gliomas in eloquent areas, but not as much for high-grade gliomas. This meta-analysis aims to determine whether the surgeon, when using ISM and AC, is able to achieve improved overall survival and decreased neurological morbidity in patients with high-grade glioma as compared to resection under general anesthesia (GA).

Methods

A systematic search was performed to identify relevant studies. Adult patients were included who had undergone craniotomy for high-grade glioma (WHO grade III or IV) using ISM (among which AC) or GA. Primary outcomes were rate of postoperative complications, overall postoperative survival and percentage of gross total resections (GTR). Secondary outcomes were extent of resection and percentage of eloquent areas.

Results

Review of 2,049 articles led to the inclusion of 53 studies in the analysis, including 9,102 patients. The overall postoperative median survival in the AC group was significantly longer (16.87 versus 12.04 months; $p<0.001$) and the postoperative complication rate was significantly lower (0.13 versus 0.21; $p<0.001$). Mean percentage of GTR was significantly higher in the ISM group (79.1% versus 47.7%, $p<0.0001$). Extent of resection and preoperative patient KPS were indicated as prognostic factors, whereas patient KPS and involvement of eloquent areas were identified as predictive factors.

Conclusions

These findings suggest that surgeons using ISM and AC during their resections of high-grade glioma in eloquent areas experienced better surgical outcomes: a significantly longer overall postoperative survival, a lower rate of postoperative complications and a higher percentage of GTR.

INTRODUCTION

Glioblastomas (WHO IV glioma) are devastating tumors with one of the worst prognoses in oncology. The median survival after surgery and combined treatment with chemo- and radiotherapy ranges from 12 to 15 months and no curative therapy is currently available[23,6]. Multiple studies show that extent of resection of the contrast enhancing part of the tumor improves survival in patients with GBM[15-18,20-22,24]. Further analyses showed that patients who previously had complete resections derived the most benefit from the temozolomide (TMZ) regimen compared with those who had had incomplete resection[1]. Thus, in addition to the survival benefit associated with maximum cytoreductive surgery such surgery seems essential for the efficacy of modern adjuvant treatment. More than 50% of GBMs are located near or in eloquent areas of the brain. Damaging these areas during surgery can lead to severe and permanent neurological deficits that seriously impact the quality of life. Therefore, when resecting GBMs in these areas, they are usually not operated as aggressive as possible, due the chance of seriously damaging the patient with a rather low life expectancy[13,15-18,20,23]. However, patients with partial or subtotal resections will benefit less from radio- and chemotherapy as compared to patients with total resections[15-18,20-22,24].

Intraoperative stimulation mapping (ISM) allows the surgeon, to prevent damage to eloquent cortical and subcortical areas during resection[2,19]. There is compelling evidence that surgeons using ISM experience increased resection percentage while preserving quality of life in low-grade glioma (LGG). We expect that the use of awake craniotomy by surgeons therefore is also of important value in the surgery of GBM, and in a similar fashion can optimize the extent of resection and preserve quality of life, thereby improving survival in these patients[2,5,7-12,14,19].

The usefullness of ISM by surgeons and its impact on neurologic outcome has been evaluated mainly for mostly low-grade gliomas or as a descriptive review. In this article, a meta-analysis is performed to compare the surgeon's use of intraoperative stimulation mapping (among which awake craniotomy, AC) versus general anesthesia for the resection of high-grade glioma.

METHODS

Search Strategy

A computer-aided search of Embase, Medline (OvidSP), Web of Science, the Cochrane Library, Pubmed and Google Scholar was performed to identify relevant studies. The search terms used were (craniotomy OR surgery OR surgical approach OR surgical patient OR

surgical technique OR brain surgery OR brain tumor OR cancer surgery OR neurosurgery OR intraoperative period) AND (wakefulness OR sedation OR conscious sedation OR consciousness OR arousal OR local anesthesia OR local anesthetic agent OR electrostimulation OR sensorimotor function OR (stimulation AND brain cortex)) AND (glioma OR brain tumor OR brain cancer OR intracranial tumor OR gliobastoma OR ((brain OR intracranial OR supratentorial OR cortex OR cortical) NEAR (tumor OR tumour OR cancer OR lesion)) NOT (conference abstract OR letter OR note OR editorial) AND (english). The publication period was restricted to Januari 1, 1990, to April 1, 2017. One reviewer (JKWG) performed the initial search in association with a biomedical information specialist of the library service of Erasmus Medical Centre, who verified the search. Reference lists of the studies were searched for additional valuable studies.

Study Selection Criteria

To be included in the meta-analysis, all studies had to have examined the effects of resective glioma surgery with or without the use of ISM by surgeons. Studies were reviewed that used resective glioma surgery to improve the prognosis in patients with high-grade glioma (WHO III-IV). Only complemented studies meeting the PICO format of this study where full-text versions were available were included. PICO (Population Intervention Comparison Outcome) restrictions were made for population (patients under 18 years old were excluded), intervention (fMRI, DTI, MSI, neuronavigation or ultrasound were not considered ISM) and outcome: eligible primary outcomes were survival, extent of resection (percentage gross total resection – GTR) and complication rate. Studies were exluded if they included patients with glioma grading other than WHO grade 3 or 4; patients under 18 years old; when the pathohistology of the tumors was not specified; when the article was of review-, editorial-, commentary-, short report- format or was a chapter in a book; and when no abstract was available (Figure 1, Flowchart).

Outcome Measures and Definitions

The primary outcome measures were the event rate of postoperative complications, overall survival and percentage GTR. Postoperative complications where noted as such as defined by colleagues de Witt Hamer et al[8]. Complications were not categorized according to severity and timing of assessment. Complications were eligible as such when they emerged postoperatively; when pre-operative symptoms worsened; or when they were part of a worsening of the patients' condition postoperatively. The percentage of patients in whom GTR was obtained according to postoperative neuroimaging was also extracted. Furthermore, data regarding patient KPS and the percentage of craniotomies concerning eloquent areas was collected. Sources related to publication, population, or management characteristics where distinguished. Publication-related characteristics were publication year; continent; and study setting. Patient population-related characteristics were mean age; and percent-

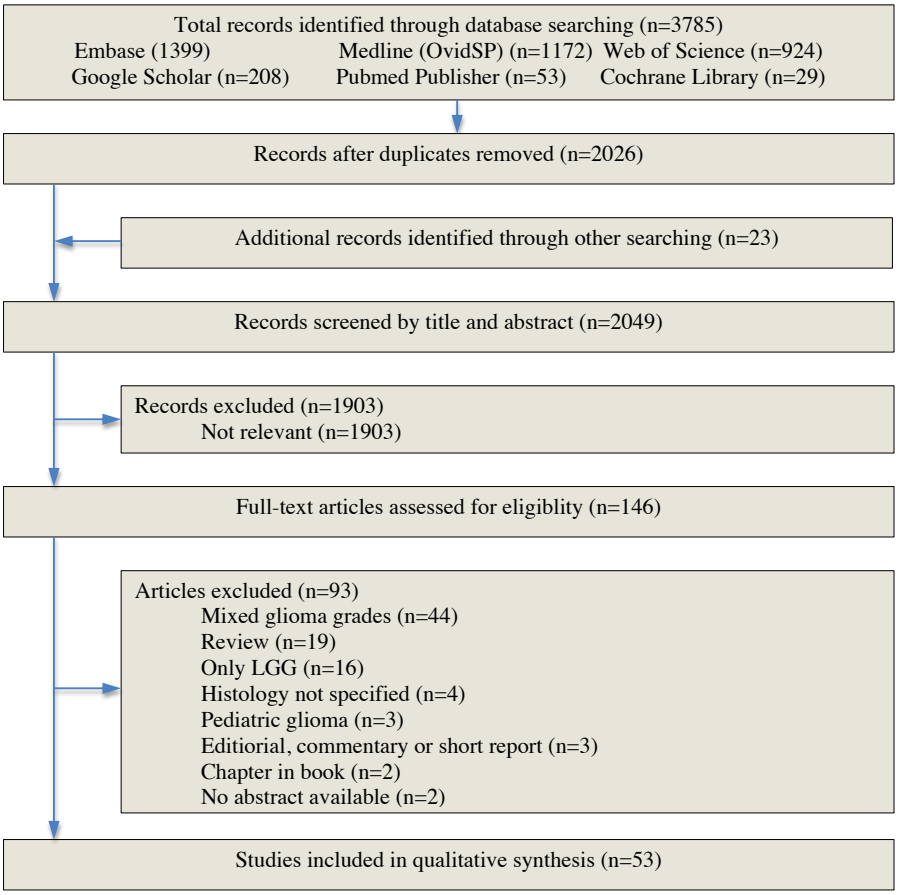


Figure 1: Flowchart

age of eloquently located gliomas. Treatment-related characteristics were intraoperative techniques; and sort of anesthesia (awake or general anesthesia). Intraoperative techniques included percentage of patients with resections using ISM. For ISM, electrocortical mapping was distinguished from motor- or somatosensory evoked potentials (MEP, SEP).

Statistical Analysis

Differences between the ISM-group (with or without AC) and GA-group for the primary outcomes were tested: 1) overall postoperative survival; and 2) rate of postoperative complications. Analysis of the the data set for primary outcomes was based on non-parametrics tests, for number of complications the Mann-Whitney test was used, whereas for survival the log-rank test was used and for the difference in percentage GTR between groups a two-tailed *t* test. No adjustment for multiple testing has been done. The significance level

was set to 5%. Forest plots were made with SPSS (Version 24.0; IBM Analytics). Analysis of the relationships between factors was done using a mixed effects regression analysis (unrestricted ML).

RESULTS

Study characteristics

The search strategy yielded 3,785 publications, of which 2,026 remained after duplicates were removed. Twenty-three additional recoreds were identified through alternative search strategies, mainly by searching the reference lists of the studies, increasing the total number of records identified to 2,049. Following screening by title and abstract, 146 articles were considered relevant and were assessed for eligibility. Review of these 146 articles led tot the inclusion of 53 studies in the analysis, including 9,102 patients. 1,260 patients were operated using ISM, 7,842 patients were operated under general anesthesia. The study characteristics of the 53 publications are listed in the Data Supplement. Not all studies allowed extraction of all end points. The complications mainly consisted of motor- and language deficits (Data Supplement). The cohorts varied between 9 and 1229 patients. Included articles were publicated between 1999 and 2016. Twenty-two articles were of European origin, twenty-one articles were of North-American origin, eight articles were of Asian origin, two articles were of South-American origin, and one article was of Middle-East origin. Forty-eight studies were performed in an university setting (91%). Eleven studies used electrostimulation (sub)cortical mapping intraoperatively. Eleven studies used evoked potentials (such as MEPs, SEPs) intraoperatively. Four studies used awake craniotomy as anesthetic modality. The mean age of the study populations differed between 49.0 and 78.0 years. Percentage of eloquently located gliomas differed between 0 and 100%. The percentage of patients in whom GTR was obtained differed between 6 and 96%. The overall postoperative median survival of patients following diagnosis differed between 4.5 and 16.3 months. Postoperative complication rates differed between 0.0 and 0.64.

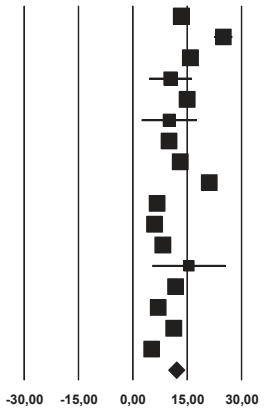
Overall survival

The median overall survival rates for each study are provided in Table 1 of the Data Supplement. Studies evaluating craniotomy under GA with data on overall survival (n=17) included 4,390 patients with a median overall survival of 12.04 months (SE=1.14; 95% CI 9.80-14.28). Studies evaluating craniotomy with ISM with available data (n=5) included 279 patients with a median overall survival of 15.53 months (SE=1.68; 95% CI 12.24-18.82). Studies evaluating awake craniotomy (subgroep of ISM) with available data (n=3) included 210 patients with a median overall survival of 16.87 months (SE=0.75; 95% CI 15.40-18.34). The median survival in the ISM group was almost 3.5 months longer than in the GA group,

but this was not significant (p=0.085). The median survival in the awake group was more than 4.5 months longer than in the GA group, which was significant (p<0.001). Forest plots for median overall survival rates are displayed in Figure 2.

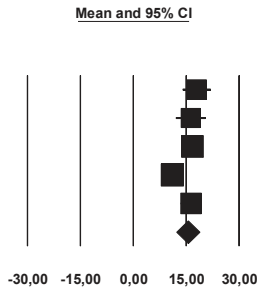
GA group

First_author	Mean	Standard error	Lower limit	Upper limit
Li	13,400	0,408	12,601	14,199
Ringel	25,000	1,247	22,556	27,444
Lacroix	15,900	0,687	14,554	17,246
Chaichana_2010	10,400	3,001	4,518	16,282
Oh	15,000	0,737	13,556	16,444
Chaichana_2014	10,050	3,887	2,432	17,668
Polin	10,000	0,914	8,208	11,792
Oszvald	13,100	0,839	11,456	14,744
Yamaguchi	21,100	1,063	19,016	23,184
Ewelt	6,700	0,958	4,823	8,577
Hoffermann	6,000	0,756	4,519	7,481
Konglund	8,300	0,703	6,921	9,679
Hassaneen	15,500	5,169	5,368	25,632
Kushnir	11,800	0,997	9,845	13,755
De Bonis	7,000	0,982	5,076	8,924
Kombos_2009b	11,300	0,693	9,942	12,658
Mandl	5,200	1,003	3,234	7,166
	12,039	1,142	9,800	14,277



ISM group

First_author	Mean	Standard error	Lower limit	Upper limit
Talacchi	18,000	2,026	14,028	21,972
Ohue	16,300	2,139	12,108	20,492
Yoshikawa	16,800	0,967	14,905	18,695
Kombos_2009a	11,100	0,621	9,883	12,317
Signorelli	16,400	1,501	13,458	19,342
	15,532	1,680	12,240	18,824



Awake group

First_author	Mean	Standard error	Lower limit	Upper limit
Talacchi	18,000	2,026	14,028	21,972
Yoshikawa	16,800	0,967	14,905	18,695
Signorelli	16,400	1,501	13,458	19,342
	16,865	0,754	15,387	18,344

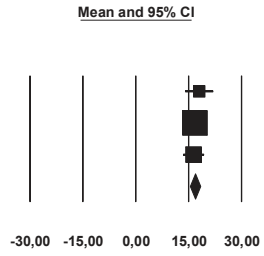


Figure 2: Forest plot

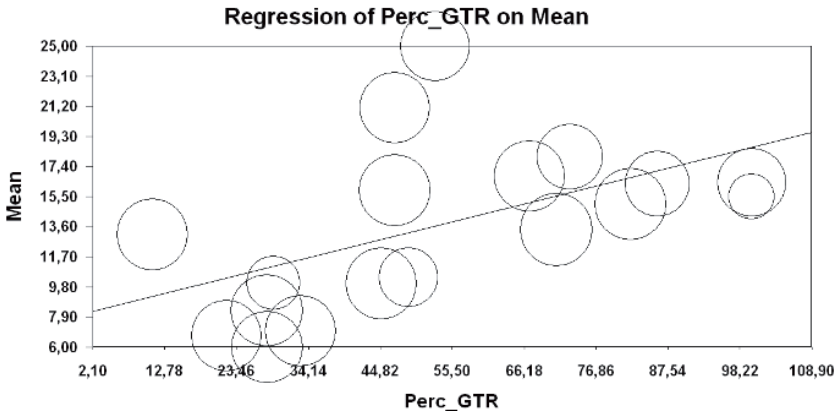


Figure 3: Extent of resection and overall survival

Extent of resection and survival

Eighteen studies evaluated the extent of resection (expressed as percentage of craniotomies in which gross total resection (GTR) was achieved) in correlation with overall survival. Percentages of craniotomies in which GTR was achieved in each study are provided in Table 1 of the Data Supplement. Using a mixed effects regression with unrestricted ML, a significant positive relation was found between extent of resection and overall survival (b=0.11; SE=0.04; p=0.012) (Figure 3), indicating extent of resection as a major prognostic factor in high-grade glioma surgery.

Preoperative patient KPS and survival

Forty-five studies evaluated preoperative patient KPS (Karnofsky Performance Score) in correlation with overall survival. Preoperative patient KPS are provided in Table 1 of the Data Supplement. Using a mixed effects regression with unrestricted ML, a significant positive relation was found between preoperative patient KPS and overall survival (b=0.61; SE=0.13; p<0.001), indicating preoperative patient KPS as a major prognostic factor in high-grade glioma surgery.

Postoperative complications

The postoperative complication rates for each study are provided in Table 1 of the Data Supplement. Studies evaluating craniotomy under GA with data on postoperative complications (n=19) included 5,826 patients with a total of 1250 postoperative complications. In this group, the postoperative complication rate was 0.21 (95% CI 0.20-0.23). Studies evaluating craniotomy with ISM with available data (n=9) included 430 patients with a total of 54 postoperative complications. In this group, the postoperative complication rate was

0.13 (95% CI 0.10-0.16). The complication rate in the ISM group was significantly lower than in the GA group (p<0.001).

Extent of resection

The extent of resection is expressed as percentage of GTR obtained for each study. The data are provided in Table 1 of the Data Supplement. Studies evaluating craniotomy under GA with data on extent of resection (n=24) included 6,880 patients. In 3,283 cases, GTR was obtained. In this group, the mean percentage of GTR was 47.7% (95% CI 40.4-55.5). Studies evaluating craniotomy with ISM with available data (n=6) included 369 patients. In 292 cases, GTR was obtained. In this group, the mean percentage of GTR was 79.1% (95% CI 69.8-88.4). The mean percentage of GTR in the ISM group was significantly higher than in the GA group (p<0.001).

Extent of resection and postoperative complications

Fifteen studies evaluated extent of resection (expressed as percentage of craniotomies in which gross total resection (GTR) was achieved) in correlation with postoperative complications. Percentages of craniotomies in which GTR was achieved in each study are provided in Table 1 of the Data Supplement. Using a mixed effects regression with unrestricted ML, no relation was found between extent of resection and overall survival (b=-0.018; SE-0.012; p=0.132) (Figure 4), indicating that achieving a higher extent of resection does not yield a higher rate of postoperative complications.

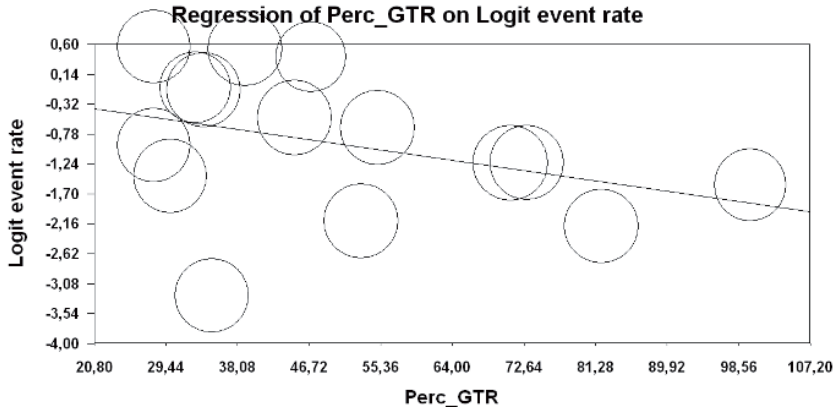


Figure 4: Extent of resection and postoperative complication rate

Patient KPS and postoperative complications

Ten studies evaluated preoperative patient KPS in correlation with postoperative complications. Percentages of eloquent areas in each study are provided in Table 1 of the Data Supplement. Using a mixed effects regression with unrestricted ML, a significant positive relation was found between patient KPS and postoperative complications (b=-0.095; SE=0.039; p=0.014), indicating preoperative patient KPS as a major predictive factor for postoperative complications in high-grade glioma surgery.

Eloquent areas and postoperative complications

Eleven studies evaluated the percentage of eloquent areas in correlation with postoperative complications. Percentages of eloquent areas in each study are provided in Table 1 of the Data Supplement. Using a mixed effects regression with unrestricted ML, no overall relation was found between the percentage of eloquent areas and postoperative complications (b=-0.009; SE=0.013; p=0.475). However, a significant relation was found when evaluating only studies investigating craniotomies under GA, indicating that a higher percentage of eloquent areas was significantly positively related with a higher postoperative complication rate (b=0.044; SE=0.007; p<0.001).

DISCUSSION

This meta-analysis shows that patients who had been operated by surgeons using AC as ISM for a single supratentorial high-grade glioma had a significant longer overall postoperative median survival (more than 4.5 months longer) and were subject of less postoperative complications in eloquent areas (0.13 versus 0.21). Furthermore, the percentage of resections in which GTR was obtained, was significantly higher in the ISM group as compared to the GA group (47.7% versus 79.1,

p<0.001). The use of ISM and AC by surgeons is safe, as a greater extent of resection did not yield a higher rate of complications. Moreover, extent of resection and preoperative patient KPS were indicated as prognostic factors, whereas patient KPS and the involvement of eloquent areas were identified as predictive factors. These results suggest that the use of ISM (AC in particular) by surgeons should be implemented as a routine operation for surgery of high-grade tumors near eloquent areas of the brain.

It is important to recognize the ifs and buts of the use of adjunct surgical techniques such as ISM and AC. The results yielded by the use of such techniques are only as good as the surgeon who uses these techniques. The fact that no technique can ever replace knowledge, experience and skill should be acknowledged, valued and acted upon accordingly. Mapping

and monitoring during glioma resections are useless if the surgeon is not familiar with using these techniques. Implementing new techniques takes practice and will inevitably come with a certain learning curve regarding both technical use and case selection.

Neurosurgeons have a daunting task: resecting the tumor with an extent as great as possible, while simultaneously minimzing the risk for postoperative complications and especially neurological morbidity. Surgeons use ISM to maximize resection, primarily to increase the patient's survival while minimizing the chances of morbidity and loss of neurological function[2,24]. AC is the most frequent used form of ISM, by using electrocortical and subcortical mapping to differ eloquent brain tissue from brain- or tumor tissue that is safe to resect. Hereby, surgeons try to maximize the extent of resection with at the same time minimizing the risk of postoperative complications. To date, surgeons use ISM and AC in particular for the resection of low-grade gliomas because of the usually near-eloquent location of these tumors[4,13]. Only few studies have evaluated the use of these techniques in high-grade gliomas, as is reflected in the studies included (see also Table 1, Data Supplement). We showed that surgeons using AC can significantly contribute to this goal by preserving the quality of life of these patients and decreasing the risk of postoperative morbidity when operating in eloquent areas, while increasing extent of resection and maximizing postoperative survival.

To the best of our knowledge, this is the first study that systematically investigates the use of ISM and AC by surgeons in high-grade glioma surgery only.

A study and meta-analysis very similar to ours, conducted by De Witt Hamer et al included 8,091 patients with supratentorial infiltrative glioma (high- and low-grade glioma) that were resected by surgeons using ISM or not[8]. They found that glioma resections in which the surgeon had used ISM were associated with fewer late major neurologic deficits. These findings are in accordance with our results evaluating high-grade glioma resections, since we found that surgeons using AC as ISM experienced decreased rates of postoperative complications in eloquent areas.

Sacko et al prospectively compared surgeons using AC versus craniotomy under GA for resection of supratentorial lesions including 575 glioma patients[19]. They found that patients with tumors in eloquent areas revealed a significantly better neurological outcome and extent of resection in the AC group than the GA group. Although this study also includes low-grade glioma patients, it is one of the largest prospective studies comparing surgeons using AC and craniotomy under GA head-to-head for postoperative outcomes in glioma surgery. We found similar results after our data analysis, suggesting a role for the use of AC by surgeons in resections for high-grade glioma – especially in eloquent areas – to improve outcomes after craniotomies.

Chaichana et al conducted a retrospective study at the Johns Hopkins University to develop a prognostic grading system in glioblastoma patients[3]. Theyfound that (among others) a poor preoperative performance status proved to be a strong prognostic factor in glioblastoma surgery. In accordance with this findings, we found that preoperative patient KPS was not only indicated as a prognostic factor, but also a predictive factor (a poor preoperative KPS indicating an increased risk of postoperative complications). These results underline the importance of identifying subgroups of patients within the high-grade glioma patient population and the role ISM/AC use by surgeons can play in optimalization of surgery outcomes.

This study should be interpreted whitin the limitations of a meta-analysis based on observational studies. The selected publications are observational or retrospective in nature and therefore subject to selection bias, publication bias and subjective outcome assesments, as mentioned before by de Witt et al[8]. We therefore advise a randomised controlled trial where awake craniotomy with ISM is compared to surgery under general anesthesia for GBM near eloquent areas. Primary outcomes should be focused on neurological morbidity and extent of resection. Furthermore, the selection bias of our findings can be expected due to patient selection with various indications for surgical intervention. However, we minimized the risk for this bias by our vast amount of data and number of included studies of patients.

CONCLUSIONS

Surgeons resecting high-grade glioma with ISM are able to achieve a higher percentage of GTR, and the use of AC by surgeons is associated with significantly longer overall postoperative survival with less postoperative complications as compared with craniotomy under GA. The greater extent of resection achieved by mapping techniques did not yield a higher rate of complications. Furthermore, extent of resection and preoperative patient KPS were indicated as prognostic factors, whereas patient KPS and the involvement of eloquent areas were identified as predictive factors. Our findings confirm preliminary findings of other authors with smaller group sizes and elaborate on large studies with both low-grade and high-grade patient cohorts. Future studies should focus on evaluating the role of the use of AC by surgeons in the treatment of high-grade glioma and optimize risk stratification using prognostic factors. Subgroups of patients should be identified that might benefit the most from extensive surgery and AC. If future studies confirm- and elaborate on the results presented in this study, the role of awake craniotomies in neurooncology should be revisited and expanded.

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Table 1a: Study characteristics

First author	Year	Mean age	Electro-stimulation (ISM)	Evoked potentials (ISM)	Conventional (GA)	Awake (AC/ISM)	% eloquent areas	% GTR	Median survival (mo) (95%CI)	Complications	Median KPS pre-op
Li	2016	55.7	0	0	1	0	38	71	13.4 (12.6-14.1)	279/1229	90
McGirt	2009	51.0	0	0	1	0	NA	35	12.3 (NA)	34/949	80
Chaichana	2009	55.0	1	1	1	0	NA	33	NA	63/648	80
Ringel	2016	57.0	0	0	1	0	NA	53	25 (22.5-27.4)	54/503	90
Sanai	2011	60.0	0	0	1	0	NA	69	12.2 (NA)	NA/500	80
Lacroix	2001	53.0	0	0	1	0	44	47	15.9 (14.6-17.3)	NA/416	80
Chaichana	2010	58.6	0	0	1	0	28	49	10.4 (4.7-16.5)	NA/393	80
McGirt	2009	54.0	0	0	1	0	NA	55	12.8 (NA)	103/306	80
Oh	2014	52.0	0	0	1	0	NA	82	15.0 (13.6-16.5)	30/301	80
Chaichana	2014	62.0	0	0	1	0	29	29	12.6 (2.4-17.7)	NA/292	90
Polin	2005	60.0	0	0	1	0	50	45	10 (9.0-11.8)	104/280	80
Ening	2015	NA	0	0	1	0	78	39	NA	159/252	70
D'Amico	2015	73.0	0	0	1	0	NA	NA	9.0 (NA)	52/243	80
Oszvald	2012	61.0	0	0	1	0	NA	11	13.1 (±12.9)	NA/234	80
Talacchi	2010	NA	1	1	0	1	100	73	18 (15.0-23.0)	39/171	80
Yamaguchi	2012	55.0	0	0	1	0	56	47	21.1 (19-23.2)	NA/160	80
Gulati	2011	62.0	0	0	1	0	NA	34	NA	67/141	70
Martinez	2007	58.3	1	1	1	0	67	82	6.0 (±4.4)	76/138	70
Chaichana	2011	73.0	0	0	1	0	25	30	7.9 (NA)	25/129	80
Grabowski	2014	60.0	0	0	1	0	24	6	13.8 (NA)	NA/128	90
Dea	2012	60.5	0	0	1	0	NA	NA	8.9 (NA)	NA/126	NA
Uzuka	2012	65.0	0	0	1	0	NA	NA	13.5 (NA)	NA/107	60

Table 1a: Study characteristics (continued)

First author	Year	Mean age	Electro-stimulation (ISM)	Evoked potentials (ISM)	Conventional (GA)	Awake (AC/ISM)	% eloquent areas	% GTR	Median survival (mo) (95%CI)	Complications	Median KPS pre-op
Ewelt	2011	70.8	0	0	1	0	NA	22	6.7 (4.8-8.1)	NA/103	70
Lorenzoni	2008	49.0	0	0	1	0	NA	NA	12.0 (NA)	12/103	NA
Hoffermann	2015	71.0	0	0	1	0	NA	28	6.0 (4.5-7.5)	27/97	70
Scott	2011	76.1	0	0	1	0	NA	25	4.5 (NA)	NA/93	NA
Keles	1999	51.0	0	0	1	0	NA	25	14.0 (NA)	NA/92	90
Shinoda	2001	57.4	0	0	1	0	44	44	13.0 (NA)	9/82	60
Konglund	2013	68.5	0	0	1	0	59	28	8.3 (6.9-9.7)	51/80	80
Uzuka	2014	78.0	0	0	1	0	NA	NA	9.8 (NA)	27/79	60
Hassaneen	2011	NA	0	0	1	0	NA	100	9.7 (5.2-25.8)	13/75	80
Marina	2011	69.0	0	0	1	0	NA	20	5.8 (NA)	NA/74	50
Muacevic	2003	69.4	0	0	1	0	NA	NA	5.5 (NA)	3/58	70
Benveniste	2005	54.9	1	1	0	0	NA	87	NA	2/54	NA
Schucht	2012	60.0	1	1	0	0	100	96	16.7 (NA)	2/53	80
Ulmer	2006	58.0	0	0	1	0	NA	NA	NA	20/50	NA
Ohue	2015	64.7	1	1	0	0	100	86	16.3 (12.0-22.5)	NA/49	80
Orringer	2012	NA	0	0	1	0	39	17	NA	NA/46	NA
Kushnir	2011	71.9	0	0	1	0	NA	NA	11.8 (±6.66)	NA/42	NA
Reithmeier	2003	NA	0	1	0	0	100	NA	NA	6/42	NA
Pastor	2013	49.8	1	1	0	0	100	67	NA	1/34	70
De Bonis	2013	59.0	0	0	1	0	NA	33	7.0 (5.0-9.0)	16/33	70
Kurimoto	2007	73.0	0	0	1	0	62	47	10.5 (NA)	18/30	70
Pontes	2013	73.0	0	0	1	0	NA	27	10.6 (NA)	NA/30	70
Bogosaljevic	2011	55.4	1	0	0	0	100	NA	NA	NA/26	80

Table 1a: Study characteristics (continued)

First author	Year	Mean age	Electro-stimulation (ISM)	Evoked potentials (ISM)	Conventional (GA)	Awake (AC/ISM)	% eloquent areas	% GTR	Median survival (mo) (95%CI)	Complications	Median KPS pre-op
Yoshikawa	2006	61.4	1	1	0	1	100	67	16.8 (14.8-18.8)	2/24	80
Kombos	2009	NA	0	1	0	0	100	NA	11.1 (9.8-12.4)	0/20	80
Kombos	2009	NA	0	0	1	0	0	NA	11.3 (9.8-12.7)	NA/20	80
Mandl	2008	52.0	0	0	1	0	NA	NA	5.2 (3.1-7.3)	7/20	70
Feigl	2010	55.0	0	1	0	0	100	64	11.0 (NA)	NA/18	90
Pirracchio	2010	73.5	0	0	1	0	NA	NA	NA	NA/17	80
Spena	2013	53.7	1	0	0	1	100	NA	NA	0/17	NA
Signorelli	2001	57.5	1	0	0	1	100	NA	16.4 (±6.36)	2/15	80
Tanaka	2012	73.0	0	0	1	0	45	NA	12.0 (NA)	1/9	80

Table 1b: Study characteristics

First author	Year	PMID reference	Country	University setting
Li	2016	26495941 J Neurosurg 2016;124:977-988	United States	1
McGirt	2009	18847342 Neurosurgery 2009;65:463-470s	United States	1
Chaichana	2009	19344222 J Neurosurg 2009;111:282-92	United States	1
Ringel	2016	26243790 Neuro-Oncology 2016;18:96-104	Germany	1
Sanai	2011	21417701 J Neurosurg 2011;115:3-8	United States	1
Lacroix	2001	11780887 J Neurosurg 2001;95:190-198	United States	1
Chaichana	2010	19817542 J Neurosurg 2010;112:997-1004	United States	1
McGirt	2009	19687690 Neurosurgery 2009;65:463-9	United States	1
Oh	2014	24553726 Acta Neurochir 2014;156:641-51	South Korea	1
Chaichana	2014	24508595 World Neurosurg 2014;82:e257-65	United States	1
Polin	2005	15739555 J Neurosurg 2005;102:276-283	United States	1
Ening	2015	25942630 Clin Neurol Neurosurg 2015;134:55-9	Germany	1
D'Amico	2015	26074434 World Neurosurg 2015;4:913-9	United States	1
Oszvald	2012	21942727 J Neurosurg 2012;116:357-64	Germany	1
Talacchi	2010	20467787 J Neurooncol 2010;100:417-26	Italy	1
Gulati	2011	22251506 World Neurosurg 2011;76:572-9	Norway	1
Martinez	2007	17963194 Zentralbl Neurochir 2007;68:176-81	Germany	1
Chaichana	2011	20887095 J Neurosurg 2011;114:587-94	United States	1
Yamaguchi	2012	22399670 Jpn J Clin Oncol 2012;42:270-7	Japan	1
Grabowski	2014	25192475 J Neurosurg 2014;121:1115-1123	United States	1
Dea	2012	22931705 Can J Neurol Sci 2012;39:632-7	Canada	1
Uzuka	2012	22976140 Neurol Med Chir (Tokyo) 2012;52:570-6	Japan	1
Ewelt	2011	20953662 J Neurooncol 2011;103:611-8	Germany	1
Lorenzoni	2008	18440602 Surg Neurol 2008;70:591-7	Chili	1
Hoffermann	2015	25462098 Clin Neurol Neurosurg 2015;128:60-9	Austria	1
Scott	2011	21363881 Neuro Oncol 2011;13:428-36	United States	1
Keles	1999	10555843 Surg Neurol 1999;52:371-9	United States	1
Shinoda	2001	11508816 J Neurooncol 2001;52:161-71	Japan	1
Konglund	2013	23432636 Acta Neurol Scand 2013;128:185-93	Norway	1
Uzuka	2014	24173683 J Neurooncol 2014;116:299-306	Japan	1
Hassaneen	2011	20690813 J Neurosurg 2011;114:576-584	United States	1
Marina	2011	21548745 J Neurosurg 2011; 115:220-9	United States	1
Muacevic	2003	12736735 J Neurol 2003;250:561-8	Germany	1
Benveniste	2005	15936381 Surg Neurol 2005;63:542-8	United States	1
Schucht	2012	22895402 Neurosurgery 2012;71:927-36	Switzerland	1
Ulmer	2006	17101902 Neurology 2006;67:1668-70	United States	1
Ohue	2015	25403686 Neurosurg Rev 2015;38:293-307	Japan	1
Orringer	2012	22978537 J Neurosurg 2012;117:851-9	United States	1

Table 1b: Study characteristics (continued)

First author	Year	PMID reference	Country	University setting
Kushnir	2011	21845970 Isr Med Assoc J 2011;13:290-4	Israel	0
Reithmeier	2003	12761674 Minim Invas Neurosurg 2003;46:65-71	Germany	1
Pastor	2013	24072425 Acta Neurochir 2013;155:2201-13	Spain	1
De Bonis	2013	22959214 Clin Neurol Neurosurg 2013;115:883-6	Italy	1
Kurimoto	2007	18159138 Neurol Med Chir (Tokyo) 2007;47:543-9	Japan	1
Pontes	2013	24472484 J Geriatr Oncol 2013;4:388-93	Brazil	1
Bogosaljevic	2011	22437285 Turkish Neurosurgery 2012;22:135-40	Serbia	0
Yoshikawa	2006	16314936 Journal of Neuro-Oncology 2006;78:91-7	Japan	1
Kombos	2009	19952567 J Clin Neurophysiol 2009;26:422-5	Germany	1
Kombos	2009	19952567 J Clin Neurophysiol 2009;26:422-5	Germany	1
Mandl	2008	18262245 Surg Neurol 2008;69:506-9	Netherlands	1
Feigl	2010	19911888 J Neurosurg 2010;113:352-7	Germany	1
Pirracchio	2010	20622683 J Neurosurg Anesthesiol 2010;22:342-6	France	1
Spena	2013	23465617 Clin Neurol Neurosurg 2013;115:1595-1601	Italy	1
Signorelli	2001	11487189 Neurol Sci 2001;22:3-10	France	0
Tanaka	2012	22875708 J Neurooncol 2012;110:227-35	United States	1

CHAPTER 4

Response to Letter to the Editor:

"Impact of intraoperative stimulation mapping on high-grade glioma surgery outcome: a meta-analysis"

Jasper K.W. Gerritsen, Arnaud J.P.E. Vincent

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Dear Editor,

We would like to thank Dr. Giussani and dr. Di Cristofori and their colleagues at the Gerardo Hospital (Monza, Italy) for their interest in our paper and we would like to clarify in this answer certain aspects of our paper as well as elaborate on our thoughts regarding the use of AC in GBM surgery.

In their letter to the editor, Dr. Giussani and Dr. Di Cristofori note potential concerns with the methodology and inclusion criteria of the studies in our meta-analysis. We agree that the absence of data on molecular markers such as MGMT status or IDH wt/mt status (the authors also mentioned the 1p19q codeletion which in our opinion is in this GBM population is of less interest) is a limitation of our study. Even though we acknowledge the importance of molecular markers in the analysis of GBM (sub)groups, we unfortunately were not able to include this in our analysis and paper because this information was not consistently mentioned in the specific literature we found for this systematic review.

We agree with Dr. Giussani and Dr. Di Cristofori that the timespan of the included studies is quite wide. We did this on purpose to present an overview of the overall evidence regarding the use of ISM in GBM surgery to its full extent. However, we included only a few papers from the pre-Stupp era (which we define as papers published in 2005 or earlier), which – as stated by the earlier mentioned authors – could have been a bias in the overall survival analysis. Looking at the data published in our Data Supplement, we can draw the conclusion that we have included 8 studies from the pre-Stupp era. Of those studies, only 3 of them contain overall survival data. The average median survival of these 3 papers combined is 13.6 months (weighted). Two of these papers included patients operated under GA without ISM, with an average median survival of 13.5 months (weighted), and one paper included patients operated with the use of ISM, with an average median survival of 16.4 months. When we compare the average median survival data of the papers from the pre-Stupp era with the overall average, we can conclude that this is in line with these survival data and would be unlikely to represent any bias (GA/without ISM: 13.5 months pre-Stupp vs. 12.0 months overall; with ISM: 16.4 months pre-Stupp vs. 16.9 months overall).

Furthermore, they state that the age of patients is higher in the group treated under GA without ISM in comparison to the group treated with ISM and that this might represent a bias in OS analysis. We agree that age is a strong prognostic factor for e.g. overall survival in GBM patients. Therefore, we further analyzed the data regarding the mean age versus overall survival in our included studies. The average age in the group treated under GA without ISM is 62.4 years (37 studies with data regarding mean age) as compared to 56.9 years in the group treated with ISM (9 studies with data regarding mean age). However,

this takes into regard all studies, with and without relevant overall survival data. When we analyze the cohort of studies that contain both mean age and overall survival data (both of these parameters we need to draw conclusions regarding differences between groups), we conclude that the mean age in the cohort of studies including patients treated with ISM (3 studies) is actually *higher* than in the cohort of studies including patients treated under GA without ISM (15 studies) (avg. age 61.2 years in the ISM group as opposed to 60.5 years in the ISM group), which is in contrast with the statement at the beginning of this paragraph and we therefore respectfully disprove it.

Dr. Giussani and Dr. Di Cristofori inquired us to elaborate on some aspects regarding the (added) value and use of AC in GBM surgery. First, they question if there are real benefits for GBM patients to have surgery with AC. We feel fortunate to say that we can state that there are many benefits in using AC in GBM surgery. In addition to our meta-analysis, we conducted a retrospective matched case-control study in our center in which we matched every patient operated under AC with 3 patients operated under GA (without ISM), including 148 patients in total[1]. We concluded that the extent of resection was significantly higher in the AC group: mean extent of resection in the AC group was 94.89% (SD = 10.57) as compared to 70.30% in the GA group (SD = 28.37) (p = 0.0001). Furthermore, the mean rate of late minor postoperative complication in the AC group (0.03; SD = -0.16) was significantly lower than in the GA group (0.15; SD = 0.39) (p = 0.05), which is in line with our meta-analysis, in which we found that patients operated with ISM experienced less late neurological complications (mean rate 0.13 (95% CI 0.20 - 0.23) vs 0.21 (95% CI 0.10 - 0.16) ($p < 0.001$). Multiple studies show that the extent of resection improves survival in GBM patients and that patients with gross-total resections (GTR) derived the most benefit from the adjuvant therapy[2-5]. However, since >50% of GBMs are located in or near eloquent areas[6], there is an increased risk of neurological morbidity when increasing extent of resection. This is in contrast with the fact that, due to the limited prognosis of these patients, preservation of quality of life in these patients should be the first concern. AC is able to increase extent of resection in GBM surgery while preserving quality of life, thereby significantly improving patient outcomes. AC could thus be of high value in the surgical treatment of GBM in eloquent areas[7-11].

Secondly, the letter's authors inquired if subcortical mapping is the only way to preserve subcortical white matter tracts during surgery, given the growth pattern of GBMs. Besides from brain mapping (during awake craniotomy) are "asleep" mapping methods another excellent tool to preserve these tracts (MEP, SSEP, continuous dynamic mapping). For example, Prof. Raabe's Neurosurgery Dept. in Bern (Switzerland) uses continuous dynamic mapping with a monopolar for GBM surgeries adjacent to motor eloquent areas[12,13]. They realize continuous (temporal coverage) and dynamic (spatial coverage) mapping by integrating the mapping probe at the tip of the suction device. Acoustic feedback indicates

proximity to the corticospinal tract. New intraoperative developments like these can be combined with ever-improving diagnostics and radiomics (DTI, HARDI, q-ball imaging) to yield optimal results in GBM surgeries in eloquent areas.
Lastly, they pose the question if an accurate microsurgical technique, aimed to circumferentially "peal", can resect the tumor mass en bloc (when possible) instead of internally aspirating it, thereby overpassing the need for AC/ISM in GBM surgery. We would like to stress that GBMs can *never* be resected radically nor circumferentially "pealed" (like, for example, in meningioma surgery) because ample evidence has shown that GBMs are characterized by leaving behind microscopic tumor satellites into the normal brain parenchyma, deeming tumor recurrences (despite maximal surgical resection followed by adjuvant chemoradiation) unfortunately inevitable[6,14]. Hence, the very essence of using AC/ISM is to enable the surgeon to determine maximal boundaries for tumor resection while preserving neurological function. As a result, an accurate microsurgical technique like the ones mentioned will fail to overpass the need for techniques in GBM surgery such as AC/ISM.
Ultimately, we agree with Dr. Giussani and Dr. Di Cristofori that GBM surgery would preferably be personalized, taking into account all the patient-, tumor- and molecular characteristics. The results of our multicenter RCT will provide vital data and results to enable the neurosurgical community to take the next step in creating a more standardized approach in the (surgical) management of GBMs. Indeed, the results of this trial will give an indication 1) if the use of AC/ISM yields superior outcomes in GBM surgery, but more specifically 2) which GBM patients will reap the most benefit from using AC/ISM.
Moreover and in line with the their last statement, we concur that creating an international, multicenter, prospective registry of intraoperative techniques in GBM surgery would be highly appreciated. We would therefore invite the letter's authors to participate in the ECRAM program. The aim of ECRAM (European Consortium and Registry for Awake surgery and intraoperative stimulation Mapping) is to collect, analyze and report clinical data of patients who have undergone GBM surgery using AC/ISM on a European scale.

Research consortia and registries like ECRAM are next to cost-effective also highly flexible, being able to incorporate numerous (surgical) techniques and parameters, and can be custom-made for each participating center. In this way, combining robust evidence of large-scale trials and registries has the potential to reach (partial) consensus about the (surgical) management of GBMs in the future.

Respectfully,

Jasper K.W. Gerritsen, MD
Arnaud J.P.E. Vincent, MD PhD

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CHAPTER 5

Awake craniotomy versus craniotomy under general anesthesia without surgery adjuncts for supratentorial glioblastoma in eloquent areas: a retrospective matched case-control study

Jasper K.W. Gerritsen, Charlotte L. Viëtor, Dimitris Rizopoulos, Joost W. Schouten, Markus Klimek, Clemens M.F. Dirven, Arnaud J.P.E. Vincent

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ABSTRACT

Background

Awake craniotomy with electrocortical and subcortical mapping (AC) has become the mainstay of surgical treatment of supratentorial low-grade gliomas in eloquent areas, but not as much for glioblastomas.

Objective

This retrospective controlled-matched study aims to determine whether AC increases gross total resections (GTR) and decreases neurological morbidity in glioblastoma patients as compared to resection under general anesthaesia (GA, conventional).

Methods

Thirty-seven patients with glioblastoma undergoing AC were 1:3 controlled-matched with one hundred eleven patients undergoing GA for glioblastoma resection. The two groups were matched for age; gender; preoperative Karnofsky Performance Score (KPS); preoperative tumor volume; tumor location; and type of adjuvant treatment. Primary outcomes were extent of resection and the rate of postoperative complications. The secondary outcome was overall postoperative survival.

Results

After matching, there were no significant differences in clinical variables between groups. Extent of resection was significantly higher in the AC group: mean extent of resection in the AC group was 94.89% (SD=10.57) as compared to 70.30% (SD=28.37) in the GA group (p=0.0001). Furthermore, the mean rate of late minor postoperative complications in the AC group (0.03; SD=-0.16) was significantly lower than in the GA group (0.15; SD=0.39) (p=0.05). No significant differences between groups were found for the other subgroups of postoperative complications. Moreover, overall postoperative survival did not differ between groups (p=0.297).

Conclusion

These findings suggest that resection of glioblastoma using AC is associated with significantly greater extent of resection and less late minor postoperative complications as compared with craniotomy under GA without the use of surgery adjuncts. However, due to certain limitations inherent to our study design (selection bias) and the absence of the use of surgery adjuncts in the GA group, we advocate for a prospective study to further build upon this evidence and study the use of AC in glioblastoma patients.

INTRODUCTION

Glioblastomas are malignant brain tumours with an annual incidence of six per 100,000. Treatment options include surgery, along with chemo(radio)therapy. Glioblastomas are of infiltrative nature, have a relatively poor radio- and chemotherapy sensitivity and are therefore invariably lethal. The median survival for glioblastoma multiforme (GBM) after treatment is approximately 15 months[1,22,25]. Due to the invasive nature of gliomas, complete resection in high grade gliomas is not possible. Surgeons strive to resect as much of the visible part of the tumor on MRI as possible, since the extent of this resection is correlated with survival and various predictive and prognostic factors[18,20,21,24]. Especially gross total resection (GTR) has been shown to increase survival in patients with high grade glioma, although at the risk of higher morbidity[14,20].

Awake craniotomy (AC) is the technique in which the patient is awake and cooperative during the resection of the tumor[2]. This allows the surgeon, together with cortical and subcortical mapping to prevent damage to eloquent cortical and subcortical areas during resection. AC is now widely used to optimalize the extent of resection while minimalising the risk of complications[3,10]. Therefore, AC is preferred over craniotomy under GA in patients with low-grade glioma in (near) eloquently located tumor[10,15,17]. However, so far, AC has not yet been implemented routinely in high grade glioma surgery, although preservation of quality of life in these patients should be the first concern due to the limited prognosis. Only very few studies have reported the use of AC in glioblastomas, but are only descriptive or studied in a systematic review which included also low grade gliomas or WHO grade 3 gliomas[6,26].

This retrospective cohort-matched study aims to determine whether AC increases the extent of resection and decreases neurological morbidity in patients with high grade glioma as compared to resection under general anesthaesia (GA).

METHODS

Anesthesia, Surgical procedure and Postoperative Management

All patients in the AC group were extensively prepared on the procedure by the anesthetist with audiovisual media. AC-patients were sedated with propofol for craniotomy and closure and completely awake during resection of the tumor. Neuronavigation was used during all resections (AC and GA). Oxygen was provided by a nose-probe, patients were spontaneously breathing throughout the whole procedure. Local anesthesia was performed with Lidocaine 1% and Bupivacaine 0.25% and Adrenaline 1:200.000 for the pins of the Mayfield clamp and Bupivacaine 0.375% with Adrenaline 1:200.000 for the surgical field.

After surgical incision, craniotomy and opening of the dura, Propofol was discontinued , allowing the patient to wake up. During the resection of the tumor, standard electrocortical and subcortical stimulation and monitoring of speech and motor function were applied to resect the glioma[7]. No adjunct preoperative diagnostics such as nTMS, DTI or fMRI were used. After resection of the tumor the patient was sedated again with Propofol until the termination of the operation.

GA patients were anesthetized with propofol, remifentanil and rocuronium, intubated and mechanically ventilated throughout the procedure. No adjuncts to surgery were used. In patients of both groups arterial blood pressure was measured invasively via the radial artery, and all patients received a urinary catheter. Mannitol, 200 ml 15% was given during the craniotomy period to all patients.

After suturing, all patients were brought to the post-anesthesia-high-care-unit, where they spent the first 24 hours postoperatively. Morphine and paracetamol were given as postoperative analgesics routinely.

Inclusion criteria

Two cohorts were selected from a database of patients with supratentorial glioblastomas surgically treated using either AC or resection under GA at our institution. All patients were treated for glioblastoma (WHO grade IV) by senior consultant neurosurgeons between January 2005 and January 2015. Both techniques were used at the institute, but neurosurgeons not familiar with AC performed tumor resection under GA. Patients were allocated to resection under GA or AC according to the expertise of the neurosurgeon. In every case, the primary surgeon was a senior neurosurgeon with >10 years of experience in glioma surgery, assisted by a neurosurgery resident. Allocation to treatment modality was not on the basis of the intrinsic growing nature of the tumor, such as how infiltrative or diffuse the tumor growed. In all cases, neuronavigation was used. Other adjuncts to surgery such as 5-ALA, intraoperative MRI or ultrasound were not used because a wider spectrum of techniques used by different neurosurgeons would impede the sufficient comparison as well as the reliablity of the results.

Inclusion criteria were as follows: 1) isolated GBM without evidence of multicentric or multifocal enhancement; 2) GBM location in eloquent area; 3) pathological diagnosis of glioblastoma multiforme (WHO Grade IV); 4) supratentorial lesion location; 5) preoperative KPS≥70; 6) elective surgery; 7) No crossover between groups, meaning that no individuals underwent craniotomy under both AC and GA. No patients whose craniotomy was started as AC were converted to GA during the procedure. Eloquent areas included were

1) Broca area 2) Wernicke area 3) primary sensory cortex/gyrus postcentralis 4) primary motor cortex/gyrus precentralis

Data collection

Patient characteristics were collected from a database and the hospital records, and presenting symptoms, neuroimaging findings, and data on (pre- and postoperative) neurological function and adjuvant treatment were documented. Preoperative KPS was assigned by the clinician at the time of evaluation and available in the chart for review in all cases. Deficits have been assessed by routine neurological examination conducted by PA's, consultants and residents both in the ICU, neurosurgical ward and outpatient clinic. Since this is a retrospective study, the professionals who assessed the complications were unknown of the fact that their findings would or could be used for scientific research and thus they had no direct personal interest in conducting the neurological examination and assessing the deficits. The deficits were noted in the patient records and directly exported from these records in our database. There was no room for any interpretation of the findings in any way.

The MRI characteristics that were recorded included the lesion's size, specific lobe involvement, presence of a hemorrhagic component, and the degree of mass effect. The lesion's size was before- and after surgery (residual tumor) manually calculated based on T1 with contrast MR images using the frequently used method described by (among others) Shah et al[19] in three directions, which was approved by the neuroradiology department.

Extent of resection (EOR) as a percentage was calculated as: (preoperative tumor volume-/-postoperative tumor volume)/preoperative tumor volume. EOR was calculated based on the contrast-enhanced tumor on T1 plus Gadolinium contrast images. Operative data were reviewed for the use of awake craniotomy with motor and langugage mapping, Postoperative complications were classified in four categories: early minor-, early major-, late minor-, and late major complications. Classification of postoperative complications was used as described in the meta-analysis of colleagues de Witt Hamer et al[6]. Assessment of complications was done by routine neurological examinations postoperatively. For assessing the severity of a paresis, the MRC muscle scale was used, grading pareses from 0 (no contraction, paralysis) to 5 (normal power). Severe deficits involve muscle strength grade 1-3 on the MRC muscle scale, aphasia or severe dysphasia, hemianopsia or a vegetative state. All other neurologic complications were considered less severe, including grade 4 monoparesis on the MRC scale, facial droop (central N. VII palsy), isolated cranial nerve deficit, dysnomia, somatosensory syndrome or parietal syndrome. The distinction between early- and a late complication was 3 months postoperatively. This cutoff point is commonly considered the usual cutoff for permanency of postoperative neurologic deficits. Late complications, even minor-, are clinically important since these communicate permanent neurological

complications from the surgery. Note that patients can experience multiple postoperative complications. To count more than one postoperative complication for one patient in the total number of complications, the complications have to occur independently from each other. However, if a patient experiences an early complication that becomes permanent, this will be counted both as an early complication and a late complication, since the complication has arisen from the surgery and has both short-term and long-term consequences. Transient early complications are naturally only stated as early complication as well.

Statistics: Matching procedure

The number of cases meeting the inclusion criteria was 37 in de AC group and 368 in the GA group. Patient characteristics of both groups before matching are shown in Tables 1 and 2 of the Data Supplement. Because the number of patients who underwent craniotomy under GA in the same study period was disproportionately higher, a controlled matched selection of cases from the entire operative pool was performed based on the well known strongest prognostics[3,8]: 1) age, 2) gender, 3) preoperative KPS, 4) preoperative tumor volume, 5) tumor location, 6) type of adjuvant treatment (none, radiotherapy, chemotherapy, chemoradiotherapy). Matching was done by a senior statistician and case selection was blinded for primary and secondary outcomes. Propensity score matching was used to match conventional to awake patients based on the covariates gender, type of adjuvant treatment, age, preoperative KPS, preoperative tumor volume, and tumor location. Balance between the conventional and awake groups was checked with summary measures of QQplots comparing the covariates in the matched groups, and optimal results were achieved with a 1:3 matching ratio. A matching ratio of 1:3 was chosen instead of 1:1 1) because of the rather small number of AC patients and to consequently improve precision and 2) because of the ample numbers of GA patients. "Whereas 1:1 matching may yield sufficiently precise estimates in large studies or studies with strong effects, we find that variable ratio, parallel balanced, 1:n nearest neighbor matching was a reasonable way to improve precision with little cost in bias"[16].

Statistics: Analysis after matching

111 cases were included in the GA cohort after matching. Patient characteristics of both groups after matching are shown in Tables 3 and 4 of the Data Supplement. After matching, differences between the AC- and GA-groups in the matched data for the primary outcomes were tested: 1) extent of resection; 2) postoperative survival; and 3) rate of postoperative complications. Analysis of the matched data set was based on non-parametrics tests, namely for the outcomes Resection and Number of Complications Mann-Whitney tests were used, whereas for median survival the log-rank test was used. No adjustment for multiple testing has been done. The significance level was set to 5%. Due to the coded outcome-blinded matching, it was not possible to specify the postoperative complications even further be-

yond the current early/late and minor/major grouping after the matching procedure (i.e. motor/language, further specification of neurologic deficits). Therefore, we chose to give an even more detailed overview of the postoperative complications *before* the matching procedure, since that data is available and gives a reliable indication of the distribution of the postoperative morbidity (Table 5, Data Supplement).

RESULTS

Baseline characteristics

The AC and GA cohorts were matched for variables that could affect the mean age, preoperative KPS, preoperative tumor volume, type of adjuvant treatment, gender and tumor location (Table 1-4, Data Supplement). Before matching, there were significant differences in mean age ($p<0.0001$) and preoperative KPS ($p=0.03$) (Table 1 and 2, Data Supplement). Preoperative tumor volume ($p=0.23$), type of adjuvant treatment ($p=0.61$), gender ($p=0.73$) and tumor location ($p=0.08$) did not differ significantly between groups (Table 1 and 2, Data Supplement). After matching, there were no significant differences between groups in mean age ($p=0.41$), preoperative KPS ($p=0.64$), preoperative tumor volume ($p=0.77$), adjuvant treatment ($p=0.89$), gender ($p=0.84$) or tumor location ($p=1.00$) (Table 3 and 4, Data Supplement). Furthermore, tumors were equally distributed between the left-right hemispheres in the groups ($p=0.41$).

Patient outcomes

Extent of resection

Resections under AC in glioblastoma patients proved to be superior to resections under GA regarding extent of resection. The mean extent of resection in the AC group was 94.89% (SD=10.57; IQR=6.76)), as compared to 70.30% (SD=28.37; IQR=44.76) in the GA group. The median extent of resection in the AC group was 100%, and 79.73% in the GA group. Table 1 and Figure 1 provide the extent of resection per group, showing significance ($p < 0.0001$, Mann-Whitney test).

Table 1: Summary statistics of extent of resection for matched groups

Variable	Levels	n	$\bar{x}$	SD	$\tilde{x}$	IQR
Resection	general anesthesia	111	70.30	28.37	79.73	44.76
	awake	37	94.89	10.57	100.00	6.76
$p < 0.0001$	all	148	76.45	27.27	87.67	36.31

Abbreviations: n = number; $\bar{x}$ = mean; $\tilde{x}$ = median; SD = standard deviation; IQR = interquartile range.

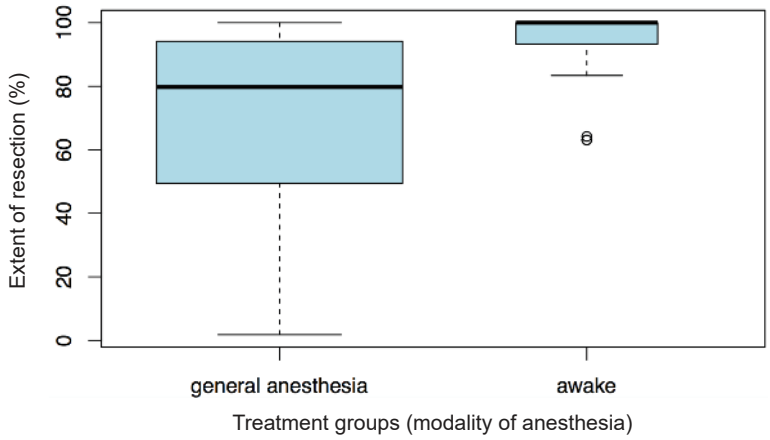

Figure 1: Box plot of extent of resection in both groups

Postoperative complications

The total number of postoperative complications in 405 patients was 260, of which 176 early- and 84 late postoperative complications. Table 5 in the Data Supplement presents the distribution of postoperative complications in all patients before matching. 16 of the 176 early postoperative complications occurred in the AC group (rate=0.43), and 160 in the GA group (rate=0.41). 3 of the 84 late complications occurred in the AC group (rate=0.081), and 81 in the GA group (rate=0.21).

Since the main objectives of AC is to minimize postoperative complications while maximizing the extent of resection, the distribution and nature of the postoperative complications is of particular interest in this group. The 16 early postoperative complications in the AC group consisted of: facial droop (central N. VII palsy) (n=5), aphasia (n=4), monoparesis grade 4 (n=3), unspecified cranial nerve deficit (n=2: N. III palsy), hemiparesis (n=1) and parietal syndrome (n=1). The 3 late postoperative complications in the AC group consisted of: hemiparesis (n=2) and monoparesis grade 4 (n=1). The AC group experienced 19 complications in total (16 early and 3 late). These 19 complications were divided over 11 patients (total: 37; rate=0.30), while 182 of the 368 patients in the GA group experienced a complication (rate=0.49).

Table 2 summarizes the rate of postoperative complications in both groups after matching (Mann-Whitney test). Complications were classified in four categories: early minor; early major; late minor; and late major. The mean rate of early minor postoperative complications in the AC group was 0.24 (SD=0.64), while this was 0.22 (SD=0.46) in the GA group (p=0.71). The mean rate of early major postoperative complications in the AC group was 0.19 (SD=0.40), as compared to 0.25 (SD=0.48) in the GA group (p=0.54). We found a

Table 2: Summary statistics of the number of postoperative complications after matching

Variable	Levels	n	$\bar{x}$	SD	$\tilde{x}$	IQR
Early minor complications	general anesthesia	111	0.22	0.46	0	0
	awake	37	0.24	0.64		
$p = 0.71$	all	148	0.22	0.51	0	0
Early major complications	general anesthesia	111	0.25	0.48	0	0
	awake	37	0.19	0.40		
$p = 0.54$	all	148	0.24	0.46	0	0
Late minor complications	general anesthesia	111	0.15	0.39	0	0
	awake	37	0.03	0.16		
$p = 0.05$	all	148	0.12	0.35	0	0
Late major complications	general anesthesia	111	0.12	0.32	0	0
	awake	37	0.05	0.23		
$p = 0.27$	all	148	0.10	0.30	0	0

Abbreviations: n = number; $\bar{x}$ = mean; $\tilde{x}$ = median; SD = standard deviation; IQR = interquartile range.

significant higher rate of late minor postoperative complications in the GA group than in the AC group: 0.15 (SD=0.39) versus 0.03 (SD=0.16) (p=0.05). The mean rate of late major postoperative complications was 0.05 (SD=0.23), and 0.12 (SD=0.32) in the GA group (p=0.27).

Median postoperative survival

Groups were compared for postoperative survival using Kaplan-Meier curves (Figure 2, Log-rank test). Median survival time in the AC group was not significant different than in the GA group: respectively 17 months (CI: 12.0 ; 36.0); as compared to 15 months (CI: 13.0 ; 18.0) in the GA group (p=0.297; χ^2=1.1).

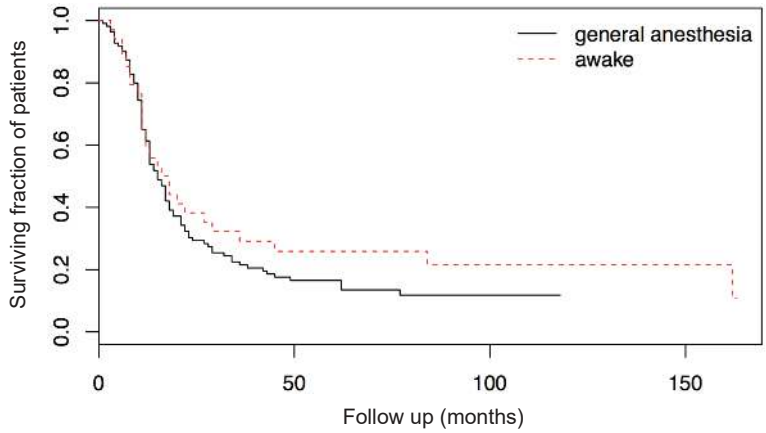

Figure 2: Kaplan-Meier curve of postoperative survival in both groups

DISCUSSION

This matched controlled study shows that patients undergoing awake craniotomy for a single supratentorial GBM had significant greater extent of resection of their tumor compared with patients undergoing resection under GA. Moreover, the rate of late minor postoperative complications in the AC group was significant lower than in the GA group. Although a higher resection percentage, no significant increase of median survival was found after AC. This could be explained by the low amount of AC patients which remained after the matching procedure.

A point of interest in our findings is the significantly lower EOR in the GA group compared to the AC group, with simultaneously a higher rate of postoperative complications. We relate this to the fact that awake craniotomy makes 1) the surgeon braver and 2) the surgery safer. AC is about maximizing the EOR while minimizing the risk of deficits. The deficits that were particularly more observed in the GA group were dysnomia and parietal syndrome. The reason for the higher incidence of dysnomia in the GA group, namely the fact that language deficits are not as definitive. The reason for the higher incidence of parietal syndrome is the fact that the possible phenotypes of this syndrome (apraxia, neglect/spatial inattention, astereognosis, agraphaesthesia etc.) are very complex in their pathophysiology in which not 'one eloquent area' or 'one part' of the brain dysfunctions, but in which rather a structure in a larger 'system' has been disrupted. Identification and disruption of parts of those systems are monitored by AC, which is unfortunately not possible with GA.

Current scientific literature

There is increasing evidence in the scientific literature that extensive resections are significant predictors of longer survival time in malignant glioma. However, a higher risk of morbidity has been reported before as the potential cost of pursuing gross-total resection (GTR)[14,18,20,21,24]. Surgical techniques have evolved, and the introduction of AC has proved to be a major stepping-stone in acquiring a greater extent of resection without an increased risk of morbidity. AC with cortical and subcortical stimulation has the advantage to control neurological function during brain tumor surgery and to increase the extent of resection in glioma surgery. However, AC has yet mainly been implemented for low-grade gliomas. Surgery of GBM is usually performed under general anesthesia (GA). Hence, resections are not as aggressive as possible, due the chance of seriously damaging the patient with a rather low life expectancy. Our results show that surgery with the AC technique can preserve quality of life of these patients by decreasing the risk of postoperative morbidity. Our data also shows that an increased resection with AC can attain improvement in prognosis in GBM patients, although we did not find a direct improvement in overall postoperative survival. There is extensive evidence since many years on the fact that not only the extent of resection, but especially resection percentages of >98% have been shown to increase significantly

overall survival[4,5,11-13,21, 23]. Also patients who previously had complete resection benefitted the most from the temozolomide regimen compared with those who had had incomplete resection (4.1 months *vs* 1.8 months overall survival[23]. Thus, in addition to the survival benefit associated with maximum cytoreductive surgery such surgery seems beneficial for the efficacy of modern adjuvant treatment.

Comparison with other studies

Other studies have found similar results regarding postoperative complications and extent of resection after AC. De Witt Hamer et al[6] conducted an extensive meta-analysis including 8,091 adult patients who had surgery for supratentorial infiltrative glioma (high and low grade glioma), with or without intra-operative stimulation mapping (ISM; e.g. awake craniotomy). They found that glioma resections using ISM were associated with fewer late major neurologic deficits and more extensive resection. Although this was a mixed group of patients, these findings are entirely in line with our results in glioblastoma patients. However, they found a significant difference in late *major* neurological deficits, where we found a significant difference in late *minor* neurological deficits. Though we do not have a conclusive reason for this, we argue that the fact that the study of De Witt Hamer included patients with low-grade and high-grade glioma, which are known to have a different (infiltrative) growing pattern which might provide a framework for interpreting our results in comparison to theirs.

Yoshikawa et al[26] conducted a study in 42 glioblastoma patients. They concluded that radical surgery with neurophysiological monitoring improved the functional outcome in glioblastoma patients. Moreover, Sacko et al[17] prospectively studied two groups of patients with supratentorial masses (n = 575), comparing AC with craniotomy under GA. They found that using AC in glioma surgery proved to be superior to craniotomy under GA regarding neurological outcome and quality of resection ($p < 0.001$). The findings from these studies are in harmony with our results. Peruzzi et al[15] add a new dimension by evaluating the length of hospital stay and impatient costs after ICU care for glioma patients who were treated with surgery under AC and GA. They concluded that patients undergoing glioma resection using AC had a significantly shorter hospital stay with reduced inpatient hospital expenses after postoperative ICU care.

In contrary to current evidence, we did not find an improvement in survival in the AC group compared to the GA group, even though the extent of resection in the AC was greatly superior. We suspect this finding to be caused by the fact that a quantitative increase in extent of resection is not enough for overall survival gain. It may be very well imaginable that a greater extent of resection would lead to an increased progression-free survival/less late complications (since more volume of the tumor was resected and symptoms will stay

away longer). However, there is evidence that only gross-total resection of the tumor yields a significant overall survival improvement (as stated before)[4,5,11-13,23]. This means that an improvement of the mean extent of resection in our AC cohort of close to 95% as opposed to just over 70% in the GA group does not necessarily yield superior overall survival outcomes. An even greater improvement, e.g. a mean extent of resection of 97-98% would possible prove more beneficial regarding survival outcome. We do acknowledge however that studying how to push the mean EOR even further to such levels would be an excellent subject for further research (e.g. by combining AC with certain adjuncts).

Statistical analysis

For the statistical analysis, we chose the Mann Whitney U test (for the outcomes extent of resection and postoperative complications) and the logrank test for survival. We would like to address the fact that the use of these statistical tests was a conscious choice, but that it would not have been the only option to analyze the results. For instance, one could argue that the use of (multivariate) regression would be appropriate to analyze the data, and we do not disagree. Our most important reason for not choosing regression is that it does not answer our research questions in the way we want them to be. For example, a regression analysis of *X, Y* with age or size as *X* and postoperative complications as *Y* gives us information about the chance of postoperative complications with a given value of *X* (age, size). This is not our research question, since we do not study the regression relationships between certain factors such as age and size on outcomes such as postoperative complications and most importantly how *Y* changes with different values of *X*. We chose logrank and not regression because we wanted to study the difference in survival between groups and not the effect of parameter *X* on survival (*Y*), for which you would use multivariate regression analysis. Therefore, matching the factors and then analyzing them with Mann-Whitney U for resection%/complications and the log-rank for survival is much more suitable to answer our research question: is there a difference between these outcomes between our two (matched) groups? Regression vs Mann Whitney U/logrank is an entirely valid discussion, but it depends for a whole lot on the research question: what do you want to study and which test would help you the best to answer this question? Secondly, we chose our approach for statistical reasons. The Mann Whitney U test is a special case of the proportional odds ordinal logistic model so you could say there is no need to turn the model around to use logistic regression. Moreover, a common rule of thumb says that regression models should have ten times as many observations as parameters, which our dataset has not. Moreover, a regression analysis is less powerful than the Mann Whitney U for detecting a difference in factors between groups. Because of the relatively small *n* in our dataset, we chose the more powerful approach.

Though, if one would be interested in studying the regression relationships in a large dataset between certain factors such as age and size on outcomes such as postoperative complications and most importantly how *Y* changes with different values of *X*, the use of a regression analysis would be fully warranted.

Limitations

Due to the broad spectrum of possible cofounders and bias in a study of this (retrospective) nature, we will discuss extensively the limitations of our study, how we might have minimized the risk of influence of these factors on our outcomes, and recommendations for further research to build on our results and strengthen the evidence by verifying or refining our findings.

(1) The first limitation of our study is the retrospective nature of this study with its additional concerns. As for comparing AC to GA, a strong selection bias could have been expected. It is difficult to adjust for and an inherent limitation. Though, we have tried to minimize the presence and influence of this bias, by 1) matching the groups; 2) matching with an 1:3 ratio to further increase precision; 3) the matching was outcome-blinded and done by an external person; 4) all resections were primarily done by the senior consultant (not the resident) with ample experience in resecting GBM in eloquent areas; 5) all resections had the purpose of GTR; 6) only a very small and dedicated team works with the neurosurgeons. However, we cannot completely exclude the chance of any selection bias. Consequently, we strongly advocate for a study of prospective nature to verify our findings.

(2) We acknowledge that some postoperative complications could have been the result of postoperative ischemia. However, since the absence of routinely performed DWI sequences in our included cases, we do not have the opportunity to present data on this subject. For a more elaborate discussion about this topic, we recommend the study conducted by Gempt and colleagues in 2013 in which they present that postoperative ischemia frequently occur in glioma patients and have an impact on postoperative neurological function[9]. Therefore, future research should take into account 1) the presence of postoperative ischemia in glioma surgery; and 2) use data regarding its effect to further improve the validity of the results.

(3) During resections in the GA group, no adjuncts to surgery were used such as 5-ALA or intraoperative MRI/ultrasound. We chose to operate the GA group without these adjuncts to study the effect of AC as neat as possible as compared to surgery under GA because we thought that adding these adjuncts to our analysis would blur the validity of the results rather than contribute to them. As in some practices the use of modern adjuncts is very common and widespread, we endorse that our study reflects the net effect of AC versus

GA, which may in some centers not necessarily render the extra improvement in surgical outcomes when compared to standard care.

Awake craniotomy and other surgery adjuncts

We are of the opinion that AC can still be of value when ioMRI and 5-ALA are already used, because all these techniques have a different purpose and therefore complement each other. ioMRI has as primary function to show the contrast-enhanced tumor residue intra-operatively (to let the surgeon see better). 5-ALA has the goal to push EOR by visualizing the tumor in the operative field in which the surgeon only gets unilateral dichotomous input: is it tumor or is it not? 5-ALA does not give any information about the functionality of the tissue. Thus, the function of 5-ALA is in a sense the same as ioMRI: to gain extent of resection by visualizing the remaining parts of the tumor. However, these adjuncts do not test functions intraoperatively. This is what AC has been designed for: positive or negative mapping to identify the functional areas and systems. In conclusion, AC still has value next to 5-ALA and ioMRI because these techniques do not exclude but complement each other: there is no contradiction to see better and to test function better.

CONCLUSIONS

Resection of glioblastoma as AC was in our study associated with significantly greater extent of resection and less minor late postoperative complications as compared with craniotomy under GA (without using other adjuncts to surgery than neuronavigation). No significant difference in median survival was found.

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DATA SUPPLEMENT

Table 1: Summary statistics of continuous variables before matching

Variable	Levels	n	$\bar{x}$	SD
Age (years)	general anesthesia	368	57.3	12.9
	awake	37	45.7	15.1
$p < 0.0001$	all	405	56.2	13.6
Preoperative KPS	general anesthesia	368	85.6	11.2
	awake	37	89.7	11.2
$p = 0.03$	all	405	86.0	11.2
Preoperative tumor volume (cm^3)	general anesthesia	368	48.06	38.90
	awake	37	66.28	64.33
$p = 0.23$	all	405	49.73	42.09

Abbreviations: n = number; $\bar{x}$ = mean; SD = standard deviation.

Table 2: Summary statistics of categorical variables before matching

Variable	Levels	n_{GA}	$\%_{GA}$	n_{awake}	$\%_{awake}$	n_{all}	$\%_{all}$
Treatment	none	32	8.7	1	2.7	33	8.2
	chemo	6	1.6	0	0.0	6	1.5
	RT	87	23.6	12	32.4	99	24.4
	chemo + RT	238	64.7	24	64.9	262	64.7
	unknown	5	1.4	0	0.0	5	1.2
$p = 0.61$	all	368	100.0	37	100.0	405	100.0
Gender	male	217	59.0	23	62.2	240	59.3
	female	151	41.0	14	37.8	165	40.7
$p = 0.73$	all	368	100.0	37	100.0	405	100.0
Tumor location	frontal	104	28.3	16	43.2	120	29.6
	parietal	74	20.1	8	21.6	82	20.2
	temporal	156	42.4	13	35.1	169	41.7
	occipital	34	9.2	0	0.0	34	8.4
$p = 0.07$	all	368	100.0	37	100.0	405	100.0

Abbreviations: chemo = chemotherapy; RT = radiotherapy; n = number.

Table 3: Summary statistics of continuous variables after matching

Variable	Levels	n	$\bar{x}$	SD
Age (years)	general anesthesia	111	48.3	14.0
	awake	37	45.7	15.1
$p = 0.41$	all	148	47.7	14.3
Preoperative KPS	general anesthesia	111	89.3	9.9
	awake	37	89.7	11.2
$p = 0.64$	all	148	89.4	10.2
Preoperative tumor volume (cm^3)	general anesthesia	111	61.95	47.97
	awake	37	66.28	64.33
$p = 0.77$	all	148	63.03	52.34

Abbreviations: n = number; $\bar{x}$ = mean; SD = standard deviation.

Table 4: Summary statistics of categorical variables after matching

Variable	Levels	n_{GA}	$\%_{GA}$	n_{awake}	$\%_{awake}$	n_{all}	$\%_{all}$
Treatment	none	5	4.5	1	2.7	6	4.0
	chemo	0	0.0	0	0.0	0	0.0
	RT	41	36.9	12	32.4	53	35.8
	chemo + RT	65	58.6	24	64.9	89	60.1
	unknown	0	0.0	0	0.0	0	0.0
$p = 0.87$	all	111	100.0	37	100.0	148	100.0
Gender	male	72	64.9	23	62.2	95	64.2
	female	39	35.1	14	37.8	53	35.8
$p = 0.84$	all	111	100.0	37	100.0	148	100.0
Tumor location	frontal	50	45.0	16	43.2	66	44.6
	parietal	23	20.7	8	21.6	31	20.9
	temporal	38	34.2	13	35.1	51	34.5
	occipital	0	0.0	0	0.0	0	0.0
$p = 1.00$	all	111	100.0	37	100.0	405	100.0

Abbreviations: chemo = chemotherapy; RT = radiotherapy; n = number.

Table 5: Summary of postoperative complications before matching

	number of patients
major neurological deficits	early – late – total
hemiparesis	18 – 8 – 26
monoparesis grade 1-3	10 – 3 – 13
aphasia	33 – 6 – 39
dysphasia	11 – 3 – 14
aphasia + hemiparesis	14 – 4 – 18
hemianopsia	19 – 4 – 23
visual field deficit unspecified	0 – 5 – 5
vegetative/deceased	1 – 4 – 5
minor neurological deficits	early – late – total
monoparesis grade 4	11 – 9 – 20
nVII palsy	19 – 3 – 22
dysnomia	6 – 17 – 23
somatosensory syndrome	9 – 1 -10
parietal syndrome	19 – 13 – 32
cranial nerve deficit	6 – 4 – 10
total nr of patients	176 – 84 – 260

CHAPTER 6

Impact of dedicated neuro-anesthesia management on clinical outcomes in glioblastoma patients: a single-institution cohort study

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ABSTRACT

Background

Glioblastomas are mostly resected under general anesthesia under the supervision of a general anesthesiologist. Currently, it is largely unkown if clinical outcomes of GBM patients can be improved by appointing a neuro-anesthesiologist for their cases. We aimed to evaluate whether the appointment of dedicated neuro-anesthesiologists improves the outcomes of these patients. We also investigated the value of dedicated neuro-oncological surgical teams as an independent variable in both groups.

Methods

A cohort consisting of 401 GBM patients who had undergone resection was retrospectively investigated. Primary outcomes were postoperative neurological complications, fluid balance, length-of-stay and overall survival. Secondary outcomes were blood loss, anesthesia modality, extent of resection, total admission costs, and duration of surgery.

Results

320 versus 81 patients were operated under the anesthesiological supervision of a general anesthesiologist and a dedicated neuro-anesthesiologist, respectively. Dedicated neuro-anesthesiologists yielded significant superior outcomes in 1) postoperative neurological complications (early: p=0.002, OR = 2.54; late: p = 0.003, OR = 2.24) ; 2) fluid balance (p<0.0001); 3) length-of-stay (p=0.0006) and 4) total admission costs (p=0.0006).

In a subanalysis of the GBM resections performed by an oncological neurosurgeon (n=231), the appointment of a dedicated neuro-anesthesiologist independently improved postoperative neurological complications (early minor: p=0.0162; early major: p=0.00780; late minor: p=0.00250; late major: p=0.0364). The appointment of a dedicated neuro-oncological team improved extent of resection additionally (p=0.0416).

Conclusion

GBM resections with anesthesiological supervision of dedicated neuro-anesthesiologists are associated with improved patient outcomes. Prospective evidence is needed to further investigate the usefulness of the dedicated neuro-anesthesiologist in different settings.

INTRODUCTION

Background

Glioblastomas (GBM) are malignant brain tumors with an annual incidence of six per 100,000. The standard treatment consist of surgery with adjuvant chemoradiotherapy. Due to GBMs infiltrative nature, they generally have a relatively poor sensitivity to adjuvant therapy and are invariably lethal. The median overall survival of GBM is approximately 15 months[1-3]. Due to the limited prognosis of these patients, considerable efforts should be aimed at preserving their quality of life (QoL) by maximizing the extent of resection while minimizing postoperative neurological deficits[4,5].

Recently, the contribution of the anesthesiologist to patient outcomes was a topic of discussion since a broad variability has been found[6]. In most countries, GBM resections are mostly performed under the supervision of a general anesthesiologist, rather than a dedicated neuro-anesthesiologist. These dedicated specialists are scheduled predominantly for more complex cases (e.g. patients with tumors that are difficult to approach or patients with notable comorbidities).

As to date, there is no research available regarding the clinical outcomes of glioma patients operated under the supervision of general anesthesiologists versus dedicated neuro-anesthesiologists. Hence, we strive to lay the framework for further research by evaluating the outcomes of these two groups of GBM patients in a large retrospective cohort of patients from our institution. We aim to determine whether the appointment of a dedicated neuro-anesthesiologist to GBM resections results in improved outcomes of these patients.

PATIENTS AND METHODS

Participants

The cohort consisted of 438 supratentorial GBM patients who had undergone tumor resection at our instition between January 2008 and July 2017. 401 patients were operated under general anesthesia (without surgical adjuncts), 37 patients were operated with intraoperative stimulation mapping using awake craniotomy (AC; no asleep mapping techniques were performed). We decided to exclude AC patients from this study, since 1) AC is used in GBM surgery, for a major part, to minimize postoperative neurological deficits, which would introduce a confounder and 2) all the AC patients were operated under the supervision of a neuro-anesthesiologist, which would introduce a bias. In all cases, neuronavigation was used. Cases performed with surgical adjuncts such as 5-ALA (5-aminolevulinic acid, Gliolan®, Specialised Therapeutics Australia) and intraoperative ultrasound were included.

No cases with intraoperative MRI were included since this modality is not available at our institution.

Eligibility criteria were: 1) isolated GBM without evidence of multicentric or multifocal enhancement; 2) pathological diagnosis of glioblastoma multiforme (WHO Grade IV); 3) supratentorial lesion; 4) preoperative KPS ≥60 and 5) planned/scheduled surgery.

Setting

All patients included in this study were operated under GA. The anesthesiologist chose one of three options for anesthesia maintenance: 1) a volatile anesthetic such as isoflurane or sevoflurane balanced with intravenous opioids; 2) TIVA (Total IntraVenous Anesthesia) with propofol and intravenous opioids; 3) a combination of a volatile anesthetic and propofol with intravenous opioids. The procedure remained constant throughout the cohort. Patients were intubated after single-bolus muscle relaxation with rocuronium or cis-atracurium and mechanically ventilated throughout the procedure. Arterial blood pressure was measured invasively via the radial artery, and all patients received a urinary catheter. Mannitol 15% was given preoperatively and/or peroperatively on discretion by the anesthesiologist or as requested by the neurosurgeon in case of relevant edema. Local anesthesia of the surgical field was performed with 10 ml lidocaine 1% and adrenaline 1:200.000. After surgical incision, craniotomy and opening of the dura, the tumor was removed using BrainLab© neuronavigation. No mapping techniques for speech or motor function using cortical or subcortical electrostimulation were used to resect the tumor. After the operation, all patients were brought to the post-anesthesia-high-care-unit (PACU), where they spent the first 24 hours postoperatively.

Procedures were allocated to dedicated neuro-anesthesiologists either in a random manner (the neuro-anesthesiologist was fortuitously the scheduled anesthesiologist for the respective case, estimated at 80-85% of cases) or specifically pre-planned (the procedure was deemed as rather difficult due to the nature of the procudure or serious comorbidities and the planning was made depending on the availability of the dedicated anesthesiologist (estimated at 15-20% of cases)). Patients were included in the general anesthesiologist group or the dedicated neuro-anesthesiologist group based on the anesthesiologist responsible for the procedure. Dedicated neuro-anesthesiologists in this study were defined as anesthesiologists who perform >75% of their clinical activities in the perioperative care for neurosurgical patients and who have followed an accredited (inter)national dedicated training or -fellowship in which they have been exposed to an expansive neurosurgical caseload both quantitatively as qualitatively as well as having developed a research niche in the subspecialty. At our institution, there are two dedicated neuro-anesthesiologists (I.E. and M.K.), with respectively more than 5 and 20 years of training as a staff member after

their dedicated training. General anesthesiologists, on the other hand, were defined as anesthesiologists who are 'allround' in their daily clinical activities and do not perform the majority of those (activities) in the care for neurosurgical patients, nor have they followed dedicated training or -fellowships or performed research in this area. They rotate every day between different subspecialities. On average, the neurosurgical caseload for a dedicated neuro-anesthesiologist in our department is around 200 cases per year, of which 120-140 brain tumor operations. For general anesthesiologists, the average neurosurgical caseload is 40-50 cases per year (mostly neurosurgical emergencies) of which <20 brain tumor operations. We also looked at dedicated oncological neurosurgeons as a variable in this study. This group is defined as neurosurgeons whose operative load consists of oncological surgery for >80%. At our institution, there are four dedicated oncological neurosurgeons with more than 15 (I.H.), 15 (J.S), 20 (A.V.) and 25 (C.D.) years of training as a staff member after their oncological neurosurgery fellowship.

Variables

Patient characteristics were retrospectively collected the hospital records and screened for presenting symptoms, preoperative patient functioning and fitness (KPS, ASA), neuroimaging findings, neurological functioning, intraoperative variables and adjuvant treatment. Ethical approval had been obtained and the requirement for written informed consent was waived by the IRB (METC Erasmus MC, Rotterdam, The Netherlands, MEC-2020-0811). The study has been conducted in compliance with the principles of the Declaration of Helsinki (2013) and the General Data Protection Regulation (GDPR) (2018). Preoperative KPS is determined routinely by the clinician at the time of evaluation. Total admission costs were calculated as: (days in PACU*PACU cost/day) + (days in neurosurgery ward*ward cost/day). The recorded MRI characteristics included the lesion's size, specific lobe involvement, multifocality, and extent of resection The lesion's size was calculated preoperatively and postoperatively manually calculated based on T1 with contrast MR images using the frequently used method described by (among others) Shah and colleagues[7], which was approved by the neuroradiology department. Extent of resection (EOR) was calculated as (preoperative tumor volume - postoperative tumor volume)/preoperative tumor volume and was calculated based on the contrast-enhanced tumor on MRI T1 + Gd contrast images. Postoperative neurological complications were classified in four categories: early minor-, early major-, late minor-, and late major complications. Classification of postoperative neurological complications was used as described in the meta-analysis of colleagues de Witt Hamer and colleagues[8]. Major complications included hemiparesis, monoparesis MRC grade 1-3, aphasia or severe dysphasia, hemianopsia, visual field deficits and vegetative state. Minor complications included monoparesis MRC grade 4, N. VII palsy, dysnomia, somatosensory syndrome, parietal syndrome or isolated cranial nerve deficit. The distinction between early- and a late neurological complication was 3 months postoperatively, which

is the usual cutoff point for permanency of postoperative neurological deficits. Postoperative neurological complications were assessed by retrospectively evaluating the electronic patient records.

Primary outcomes were 1) postoperative neurological complication rate, 2) fluid balance (ml deviating from zero), 3) length-of-stay (LOS) and 4) overall survival (months). Secondary outcomes were blood loss (ml), anesthesia modality, extent of resection (%), total admission costs (EUR) and OR duration (min).

Statistical methods

Statistical analyses were executed in collaboration with a senior statistician from the Department of Biostatistics of our own institution. Differences between the patients receiving anesthesia from a general anesthesiologist or a dedicated neuro-anesthesiologist for the primary and secondary outcomes were tested with univariate analyses. For statistically significant outcomes a multivariate analysis was performed in addition to the univariate analysis to minimize the risk for confounders and selection bias. Subgroup analyses were done for the appointment of a neuro-anesthesiologist and a oncological neurosurgeon to GBM cases. Analyses of differences between two groups in baseline characteristics for continuous variables were done using the two-tailed *t* test for independent samples. For categorical variables, the chi-square (χ^2) test was used. Analysis of the data set for outcomes based on continuous variables was done using the Kruskal-Wallis test, whereas for categorical variables the Fisher-exact test was used. Analysis of overall survival was done with the log-rank test. Significant outcomes in the univariate analysis were further analysed using a multivariate analysis using standard logistic regression. The multivariate analysis consisted of well known predictive factors in glioblastoma patients: 1) age; 2) gender; 3) preoperative KPS; 4) tumor location and 5) preoperative tumor volume. For the comparison of multiple subgroups regarding the composition of the performing team, the one-way analysis of variance (ANOVA) test was used for continous variables and the chi-square (χ^2) test for categorical variables. The significance level for all tests was set to 5%.

RESULTS

Baseline characteristics

After exluding all awake cases (n=37), a total of 401 patients were included in the cohort. All of the included patients had undergone GBM resection under general anesthesia. 320 patients were operated with anesthesiological supervision by a general anesthesiologist (GA-group), whereas in 81 patients a dedicated neuro-anesthesiologist provided anesthesia care (NA-group). Baseline patient characteristics for both groups are shown in Table 1. No significant differences in baseline characteristics between groups were observed for

Table 1: Baseline characteristics

Characteristic	Neuro-anesthesiologist	General anesthesiologist	*P* value
Total *n* patients	81	320	
Demographics			
Mean age (yrs)	59.2	58.6	$p = 0.699$
Range	19-80	18-80	
Gender			$p = 0.231$
Male (%)	53 (65.4)	186 (58.1)	
Female (%)	28 (34.6)	134 (41.9)	
Adjuvant treatment (%)			
Chemoradiation	55 (67.9)	199 (62.2)	$p = 0.373$
Chemotherapy	3 (3.7)	4 (1.3)	
Radiation	17 (21.0)	79 (24.7)	
None	5 (6.2)	34 (10.7)	
Unknown	1 (1.2)	4 (1.3)	
Tumor volume			
Mean tumor volume in mm3 (SD)	63663 (49111)	54064 (44049)	$p = 0.0878$
Tumor location – lobe (%)			
Frontal	22 (27.2)	138 (30.2)	$p = 0.632$
Parietal	17 (21.0)	91 (19.9)	
Temporal	38 (46.9)	190 (41.6)	
Occipital	4 (4.9)	38 (8.3)	
Tumor location – hemisphere (%)			
Right	41 (50.6)	214 (46.8)	$p = 0.529$
Left	40 (49.4)	243 (53.2)	
Tumor location – eloquent areas (%)	53 (65.4)	178 (55.6)	$p = 0.138$
Patient performance			
Median preoperative KPS (range)	90 (60-100)	90 (60-100)	$p > 0.05$
Median ASA score (range)	II (I-III)	II (I-III)	$p > 0.05$
Dedicated oncological neurosurgeon (%)	49 (60.5%)	182 (56.9%)	$p = 0.559$
Surgical adjuncts			
5-ALA fluorescence	6 (7.4%)	9 (2.8%)	$p = 0.0891$
Intraoperative ultrasound	12 (14.8%)	17 (5.3%)	$p = 0.0102$

demographics, adjuvant treatment, preoperative tumor volume, tumor location, proportion of eloquent areas, preoperative patient performance (KPS and ASA scores), proportion of resections done by a dedicated oncological neurosurgeon or the use of 5-ALA fluorescence. A significant difference was found for the use of intraoperative ultrasound, which was used more frequently in the neuro-anesthesia group (14.8% vs. 5.3%; p = 0.0102).

Primary outcomes

First, patients in the NA-group experienced less postoperative neurological complications (Tables 2 and 3). Early major complications were less frequent in the NA-group than in the GA-group (13.6% and 28.8%; p=0.0045, overall multivariate analysis: p=0.002, OR=2.54,

Table 2: Primary and secondary outcomes

Variable	Anesthesiologist	*n* total	Neuro-anesthesiologist (SD)	General anesthesiologist (SD)	Univariate analysis	Multivariate analysis		
					P value	*P* value	SE	*t* value
Mean fluid balance (ml)	neuro-anesthesiologist general anesthesiologist all	77 309 386	-232.1 (11.2)	538.3 (11.2)	$p < 0.0001$	$p < 0.001$	112.0	6.41
Mean LOS (days)	neuro-anesthesiologist general anesthesiologist all	81 320 401	6.3 (3.8)	7.8 (4.8)38.90	$p = 0.0006$	$p = 0.011$	0.57	2.54
Mean total admission costs (EUR)	neuro-anesthesiologist general anesthesiologist all	81 320 401	4709.0 (1927.7)	5471.3 (2432.6)	$p = 0.0006$	$p = 0.011$	289.28	2.54
Total amount of propofol (mg)	neuro-anesthesiologist general anesthesiologist all	72 81 153	1844.0 (993.1)	2151.0 (922.5)	$p = 0.005$	$p = 0.028$	152.68	2.21
Mean extent of resection (%)	neuro-anesthesiologist general anesthesiologist all	81 320 401	74.1 (24.6)	68.4 (27.0)	$p = 0.15$			
Mean OR duration (min)	neuro-anesthesiologist general anesthesiologist all	80 320 400	219.6 (64.3)	233.1 (71.8)	$p = 0.31$			
Mean amount of blood loss (ml)	neuro-anesthesiologist general anesthesiologist all	77 309 386	394.4 (337.2)	445.7 (733.5)	$p = 0.78$			
Median overall survival (months)	neuro-anesthesiologist general anesthesiologist all	80 320 400	13 (95% CI: 11-18)	13 (95% CI: 12-16)	$p = 0.17$			

Table 3: Summary statistics of anesthesia modality and neurological complication profile specified by anesthesiologist

Factor		*n* total	Neuro-anesthesiologist	General anesthesiologist	Univariate analysis	Multivariate analysis		
						P value, Odds ratio	SE	*z* value
Anesthesia modality	anesth.vap/comb	82	34	48				
	TIVA	319	47	272		$p < 0.0001$		
	all	401	81	320	$p < 0.0001$	OR = 3.97	0.280	4.93
Early complications	No	225	59	166				
	Yes	176	22	154				
	Minor	73	11	62	$p = 0.227$			
	Major	103	11	92	$p = 0.0045$	$p = 0.002$		
	all	401	81	320	$p < 0.0003$	OR = 2.54	0.300	3.11
Late complications	No	193	58	135				
	Yes	208	23	185				
	Minor	109	10	99	$p = 0.0008$			
	Major	99	13	86	$p = 0.044$	$p = 0.003$		
	all	401	81	320	$p < 0.0001$	OR = 2.24	0.276	2.92

Table 2). This was also the case for late minor- and late major complications: 12.3% late minor complications in the NA-group versus 30.9% in the GA group (p=0.0008); 16.0% late major complications in the NA-group versus 26.9% in the GA group, (p=0.044), overall multivariate analysis: p=0.003, OR=2.24, Table 2). However, early minor complications did not differ between groups (p=0.227).

Neurological complications were specified by severity, timing and type of anesthesiologist (Table 4). Notably, late postoperative complications were in the GA group more frequently permanent (53.0%) than in the NA group (30.4%) (p=0.0414). Moreover, neurological complications were specified by year (Figure 1), which also shows that the fraction of resections done under the supervision of a dedicated neuro-anesthesiologist steadily rose over the years. From 2005-2011, less than 10% of GBM resections each year were led by a dedicated neuro-anesthesiologist. From 2012-2014 this number increased from 17 to 47% and remained constant thereafter. Over the years, the incidence of early minor-, early

Table 4: Postoperative neurological complications specified by severity, timing and type of anesthesiologist

	Neuro-anesthesiologist Early (%)	**Neuro-anesthesiologist Late (%)**	**General anesthesiologist Early (%)**	**General anesthesiologist Late (%)**
				$p = 0.0045$
		$p = 0.227$		
Minor complications	**11 (13.6%)**	**10 (12.3%)**	**62 (19.4%)**	**99 (30.9%)**
Monoparesis grade 4	4 (4.9%)	2 (2.5%)	10 (3.1%)	11 (3.4%)
N. VII palsy	0 (0.0%)	1 (1.2%)	14 (4.4%)	26 (8.1%)
Dysnomia	2 (2.5%)	2 (2.5%)	9 (2.8%)	20 (6.3%)
Somatosensory syndrome	3 (3.7%)	2 (2.5%)	15 (4.7%)	22 (6.9%)
Parietal syndrome	2 (2.5%)	3 (3.7%)	10 (3.1%)	13 (4.1%)
Cranial nerve deficit	0 (0.0%)	0 (0.0%)	4 (1.3%)	7 (2.2%)
				$p = 0.044$
		$p = 0.0008$		
Major complications	**11 (13.6%)**	**13 (16.0%)**	**92 (28.8%)**	**86 (26.9%)**
Hemiparesis	1 (1.2%)	2 (2.5%)	22 (6.9%)	18 (5.6%)
Monoparesis grade 1-3	3 (3.7%)	0 (0.0%)	7 (2.2%)	4 (1.3%)
Aphasia	4 (4.9%)	4(4.9%)	28 (8.8%)	25 (7.8%)
Dysphasia	2 (2.5%)	0(0.0%)	6 (1.8%)	6 (1.9%)
Hemianopsia	1 (1.2%)	1(1.2%)	15 (4.7%)	7 (2.2%)
Visual field deficit unspecified	0 (0.0%)	3 (3.7%)	13 (4.1%)	20 (6.3%)
Vegetative/deceased	0 (0.0%)	3 (3.7%)	1 (0.3%)	5 (1.6%)
	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Permanent		**7 (30.4%)**		**98 (53.0%)**
				$p = 0.0414$
New		**16 (69.6%)**		**87 (47.0%)**
				$p = 0.0276$
Total		**23 (100%)**		**185 (100%)**

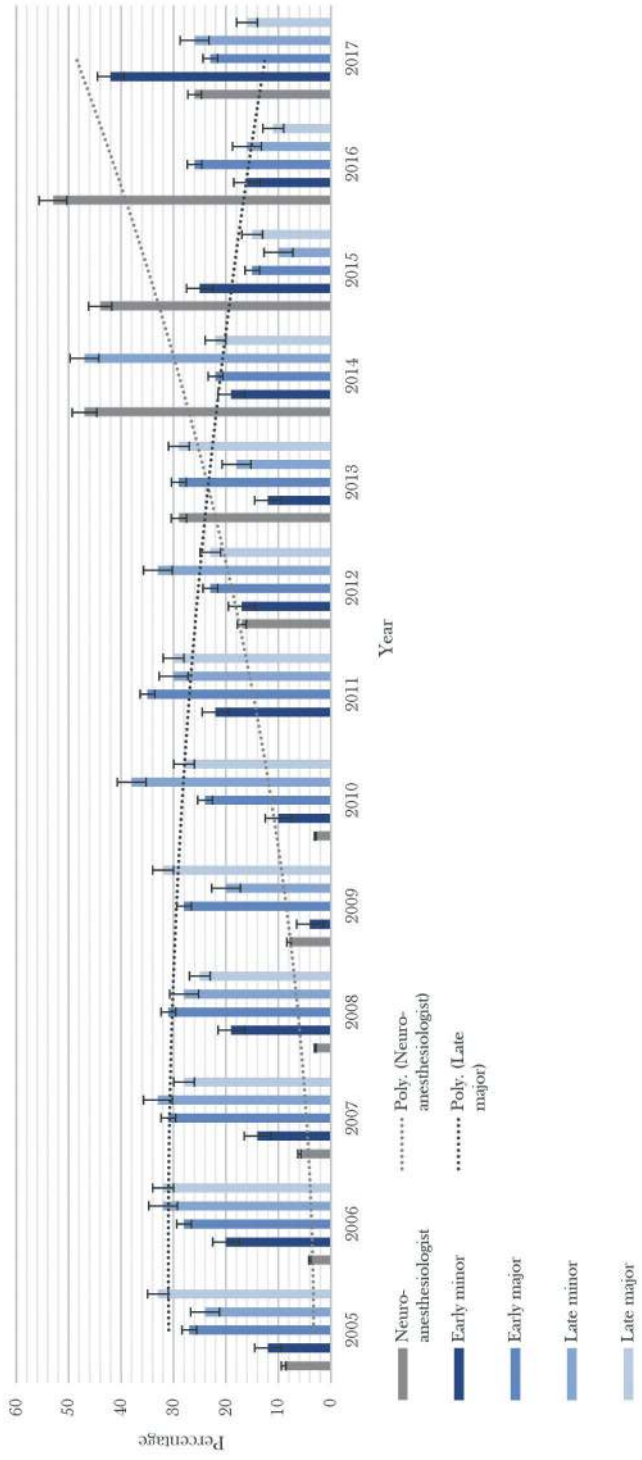

Figure 1: Postoperative neurological complications specified by severity and year

major- and late minor complications remained stable. However, the incidence of late major complications decreased from around 30% to 10-15%.

Second, fluid management was significantly controlled more strictly (defined as a balance close to 0 or slightly negative) in operations when a dedicated neuro-anesthesiologist was responsible: the mean fluid balance was -232.1 ml in those operations, whereas this was +538.3 ml when a general anesthesiologist was responsible ($p<0.0001$, multivariate analysis: $p<0.001$) (Table 2).

Third, after operations for which a dedicated neuro-anesthesiologist was appointed, patients were discharged from the hospital sooner: they stayed on average 6.3 days in the hospital versus on average 7.8 days after a operation led by a general anesthesiologist (LOS) ($p=0.0006$, multivariate analysis: $p=0.011$) (Table 2).

Fourth, postoperative overall survival did not differ between groups: both groups had a median OS of 13 months (95% CI: 11-18 months in the neuro-anesthesiology group vs. 12-16 months in the general anesthesiology group).

Secondary outcomes

General anesthesiologists use different anesthesia maintenance techniques than neuro-anesthesiologists: they used TIVA or a volatile anesthetic, whereas neuro-anesthesiologists used a combination of a volatile anesthetic with TIVA significantly more frequently ($p<0.0001$). The total admission costs per patient were significantly lower in the neuro-anesthesiology group: 4709.0 EUR (SD=1927.7 EUR) compared to 5471.3 EUR (SD=2432.6 EUR) ($p=0.0006$, multivariate analysis: $p=0.011$) (Table 2). No statistically significant differences were observed between the neuro-anesthesiology and general anesthesiology groups for 1) blood loss (393.4 ml versus 445.7 ml, $p=0.78$); 2) mean OR duration (219.6 ±64.3 min versus 233.1 ±71.8 min, $p=0.31$) and 3) extent of resection (on average 74.1% versus 68.4%, $p=0.15$).

Subgroup analysis

To evaluate the effect of the appointment of a neuro-anesthesiologist or a oncological neurosurgeon to GBM resections, we performed a subgroup analysis. Tables 5 and 6 show the baseline characteristics and surgical outcomes of all four subgroups. Subgroup 1 (n=49) consist of the GBM resections performed by dedicated neuro-anesthesiologist with an oncological neurosurgeon. Subgroup 2 (n=182) consist of the GBM resections performed by a general anesthesiologist with an oncological neurosurgeon. Subgroup 3 (n=31) consists of the GBM resections performed by a neuro-anesthesiologist with a non-oncological neurosurgeon. Subgroup 4 (n=139) consists of the GBM resections performed by a general

Table 5: Baseline characteristics and surgical outcomes for selected subgroups

Factor	Subgroup 1 Neuro-anesthesiologist + Oncological neurosurgeon	Subgroup 2 General anesthesiologist + Oncological neurosurgeon	Subgroup 3 Neuro-anesthesiologist + Non-onco neurosurgeon	Subgroup 4 General anesthesiologist + Non-onco neurosurgeon	*P* value
Total *n* patients	49	182	31	139	
Demographics					
Mean age (yrs)	59.3	58.4	58.5	58.8	$p = 0.969$
Gender					$p = 0.321$
Male (%)	32 (65.3%)	111 (61.0%)	21 (67.7%)	75 (54.0%)	
Female (%)	17 (34.7%)	71 (39.0%)	10 (32.2%)	64 (46.0%)	
Adjuvant treatment (%)					$p = 0.0101$
Chemoradiation	36 (73.5%)	113 (62.1%)	19 (61.3%)	86 (61.9%)	$p = 0.480$
Chemotherapy	1 (2.04%)	2 (1.10%)	2 (6.45%)	2 (1.44%)	$p = 0.208$
Radiation	10 (20.4%)	49 (26.9%)	7 (22.6%)	30 (21.6%)	$p = 0.641$
None	1 (2.04%)	17 (9.34%)	3 (9.68%)	17 (12.2%)	$p = 0.222$
Unknown	1 (2.04%)	1 (0.549%)	4 (12.9%)	3 (2.16%)	$p = <0.001$
Tumor volume					
Mean tumor volume in mm3 (SD)	64244 (53909)	58024 (50065)	62774 (41510)	48842 (34041)	$p = 0.103$
Tumor location – lobe (%)					$p = <0.001$
Frontal	14 (28.6%)	62 (34.1%)	8 (25.8%)	62 (44.6%)	$p = 0.0638$
Parietal	15 (30.6%)	36 (19.8%)	2 (6.45%)	37 (26.6%)	$p = 0.0356$
Temporal	19 (38.8%)	70 (38.5%)	19 (61.3%)	24 (17.3%)	$p = <0.001$
Occipital	1 (2.04%)	14 (7.69%)	3 (9.68%)	15 (10.8%)	$p = 0.278$
Tumor location – hemisphere (%)					$p = 0.0559$
Right	27 (55.1%)	88 (48.4%)	23 (74.2%)	70 (50.4%)	
Left	22 (44.9%)	94 (51.6%)	8 (25.8%)	69 (49.6%)	
Tumor location – eloquent areas (%)	32 (65.3%)	114 (62.6%)	20 (64.5%)	69 (49.6%)	$p = 0.0664$
Patient performance					
Median preoperative KPS (range)	90 (60-100)	80 (60-100)	90 (70-100)	80 (60-100)	$p = 0.145$
Median ASA score (range)	II (I-III)	II (I-III)	II (I-III)	II (I-III)	$p = 0.376$
Surgical adjuncts					
5-ALA fluorescence	4 (8.2%)	15 (8.2%)	1 (3.2%)	3 (2.2%)	$p = 0.098$
Intraoperative ultrasound	9 (18.4%)	8 (4.4%)	4 (12.9%)	5 (3.6%)	$p = <0.001$

Table 6: Baseline characteristics and surgical outcomes for selected subgroups

Factor	Subgroup 1 Neuro-anesthesiologist + Dedicated surgeon	Subgroup 2 General anesthesiologist + Dedicated surgeon	Subgroup 3 Neuro-anesthesiologist + Non-dedicated surgeon	Subgroup 4 General anesthesiologist + Non-dedicated surgeon	*P* value
Postoperative neurological complications					
		$p = 0.0162$	$p = 0.6235$		
Early minor (%)	6 (12.2%)	40 (22.0%)	5 (16.1%)	21 (15.0%)	$p = 0.195$
		$p = 0.00780$	$p = 0.6235$		
Early major (%)	6 (12.2%)	57 (31.3%)	5 (16.1%)	35 (25.2%)	$p = 0.0272$
		$p = 0.00250$	$p = 0.0440$		
Late minor (%)	5 (10.2%)	58 (31.9%)	5 (16.1%)	41 (29.5%	$p = 0.00955$
		$p = 0.0364$	$p = 0.5572$		
Late major (%)	7 (14.3%)	53 (29.1%)	6 (19.3%)	33 (23.7%)	$p = 0.150$
		$p = 0.0416$	$p = 0.137$		
Mean EOR (SD)	77.4 (20.7)	68.9 (26.8)	69.0 (29.3)	67.7 (27.5)	$p = 0.174$
		$p = <0.001$	$p = 0.938$		
Mean fluid balance [ml] (SD)	-224.9 (913.2)	415 (834.0)	-242.2 (1028.2)	705.95 (881.8)	$p < 0.0001$
		$p = 0.0656$	$p = 0.550$		
Mean LOS [days] (SD)	6.5 (4.5)	8.0 (5.1)	6.0 (2.3)	7.5 (4.4)	$p = 0.0527$
		$p = 0.0983$	$p = 0.886$		
Mean total admission costs [EUR] (SD)	4461.5 (2566.4)	5194.6 (2789.5)	4390.7 (1360.5)	5145.5 (2363.4)	$p = 0.137$
		$p = 0.0386$	$p = 0.903$		
Total amount of propofol [mg] (SD)	1856.2 (1147.0)	2192.3 (963.7)	1827.0 (744.3)	2058.6 (833.8)	$p = 0.241$

anesthesiologist with a non-oncological neurosurgeon. No significant differences in baseline characteristics were found for demographics, preoperative tumor volume, tumor location, proportion of resections in or near eloquent areas, preoperative patient functioning (KPS and ASA scores) and the use of 5-ALA fluorescence. Significant differences were found for adjuvant treatment (for 4 patients their adjuvant treatment was unknown in subgroup 3, in comparison with 1, 1 and 3 patients in subgroups 1, 2 and 4;, $p<0.001$), lobe (different distribution of parietal and temporal lobes in subgroups, $p<0.001$), and use of intraoperative ultrasound (significantly more often in the subgroups with a neuro-anesthesiologist, $p<0.001$). The subgroup analysis illustrates the primary and secondary outcomes between selected subgroups, based on the appointed neurosurgeon and anesthesiologist for the case. When evaluating the GBM resections performed by an oncological neurosurgeon (subgroups 1 and 2, n=231), the addition of a dedicated neuro-anesthesiologist to a GBM resection improved postoperative neurological complications ($p=0.0162$ for early minor deficits; $p=0.00780$ for early major deficits; $p=0.00250$ for late minor deficits and $p=0.0364$ for late major deficits), EOR ($p=0.0416$) and amount of propofol administered ($p=0.0386$) significantly. In contrast, a subanalysis of the GBM resections performed by a dedicated neuro-anesthesiologist (subgroups 1 and 3, n=81) showed that the addition of a oncological neurosurgeon had no significant effect on these outcomes. Notably, mean extent of resection and rate of postoperative complications were not significantly higher among patients in the NA-groups (subgroups 1 and 3) who were operated with the use of intraoperative ultrasound (ioUS). The mean EOR in subgroup 1 was 81.3% (SD=18.62) for patients operated with ioUS vs. 76.4% (SD=21.22) for patients operated without ioUS, $p=0.741$. In subgroup 3, the mean EOR was 62.5% (SD=37.91) for patients operated with ioUS vs. 70.1% (SD=28.79) for patients operated without ioUS, $p=0.757$). For patients operated with ioUS in subgroup 1, the rate of early minor and early major postoperative complications were 11.1% (versus 12.5% without ioUS, $p=0.904$), whereas the rates of late minor and late major postoperative complications were 0% and 11.1% respectively (versus 10.2% ($p=0.317$) and 15.0% ($p=0.764$) without ioUS). For patients operated with ioUS in subgroup 3, the rates of early minor and early major postoperative complications were 25.0% and 50.0% respectively (versus 14.8% ($p=0.603$) and 11.1% ($p=0.0488$) without ioUS), whereas the rate of late minor and late major postoperative complications was 0% (versus 18.5% ($p=0.347$) and 22.2% ($p=0.294$) without ioUS).

DISCUSSION

Key results

We investigated the added value of a dedicated neuro-anesthesiologist for GBM resections in a cohort of more than 400 patients, which makes it the most extensive and comprehensive

study about this subject to date. We found that patients undergoing resection for a single supratentorial glioblastoma under the anesthesiological supervision of a dedicated neuro-anesthesiologist 1) experienced, on average, less postoperative neurological complications 2) had their fluid balance controlled more strictly and 3) had a shorter postoperative length of stay which directly resulted in lower total admission costs of the operation.

From 2008 to 2017, an increasing number of GBM resections was led by a neuro-anesthesiologist. Simultaneously, the incidence of early minor, early major and late minor complications remained virtually stable during these years. However, the incidence of late major complications decreased dramatically, from more than 33% in 2005 to 10-15% in the last few years. This might suggest that the implementation of dedicated neuro-anesthesia in GBM resections may be one of the factors that is associated with the decreasing incidence of these neurological complications. Other factors that may contribute to this trend include the improvement in surgical protocols (e.g. increasing use of surgical adjuncts such as 5-ALA and intraoperative ultrasound) and anesthesiological protocols. Our subanalyses suggest that appointing a dedicated neuro-anesthesiologist to GBM cases, irrespective of the expertise of the neurosurgeon (oncological versus non-oncological), provides an added benefit with regard to perioperative and postoperative outcomes,.

Interpretation

Modern medicine is increasingly developing from specialization towards superspecialization due to the rapid expansion of specialized knowledge in various medical specialities. This holds true for the whole spectrum of medical professionals and is not only limited to adult anesthesiological care. Despite this revolution of speciality and superspeciality in many specialities – including neuroscience and neurosurgery – anesthesiologists are not superspecializing at the same pace[9,10].

Recently, neurosurgical patients, in particular, have a higher risk of negative outcomes than patients from other disciplines in cases of handovers of the anesthesia care[11]. Anesthesiologists should take note of the recently published neurosurgeons' wish of "dear anesthesiologist, please don't abandon us"[12] and in response, provide a continuum of care to every patient, but especially to the GBM patient to optimize their still quite poor outcomes. In 2014, Dr. Ghaly described in his work (published at the SNACC meeting in San Francisco) 'fifteen reasons that ask for immediate neuroanesthesia commitment and growth in neuroscience' and the usefulness of a similarly dedicated neuro-care team has already been demonstrated in various studies[13-16]. The main argument for the necessity of these neuro-teams is that the care of the critically ill neurologic patient requires specific training.

We tested different hypotheses to explain why GBM patients who had undergone a resection under the supervision of a neuro-anesthesiologist experienced less postoperative complications than patients in the general anesthesiologist group. Generally, GBM surgery means balancing between maximizing the extent of resection while preventing neurological morbidity as much as possible. Therefore, the lower incidence of *early* postoperative complications in the NA-group could have been explained by a safer resection (mapping techniques, for example), or a less extensive resection. Likewise, the lower incidence of *late* postoperative complications in the NA-group could have been explained by a higher extent of resection, potentially resulting in a longer progression-free survival. Since a) the mean extent of resection was not significantly different between the NA-group and GA-group, and b) all patients had been operated without neurophysiological mapping techniques, none of these possible explanations proved to be viable at first.

In order to evaluate the NA-group and GA-group in further detail, we divided each group in two subgroups based on the appointed surgeon (oncological neurosurgeon versus non-oncological neurosurgeon), which resulted in a total of four patient subgroups. We found that the addition of a neuro-anesthesiologist to a GBM resection, irrespective of the surgeon, led to two results that were most notable: 1) less postoperative complications, 2) a higher prevalence of ioUS use (5-ALA use was comparable for all subgroups). Moreover, the combination of a neuro-anesthesiologist with a dedicated oncological surgeon (subgroup 1) led to a higher extent of resection. These results indicate that the appointment of a neuro-anesthesiologist certainly helps in achieving a maximum safe resection and that a dedicated neuro-oncological team yields optimal results.

To analyze whether ioUS could explain the lower incidence of postoperative complications in the NA-group, we further evaluated all patients operated with the use of ioUS in both NA-subgroups. We found that mean extent of resection and rate of postoperative complications did not differ between patients operated with or without ioUS in both NA-subgroups (with the exception of late minor complications in subgroup 3 with a p-value of 0.0488 which has to be interpreted with caution regarding the low *n* of ioUS patients in that subgroup). We therefore deem it unlikely that the lower incidence of postoperative complications in the NA-group is the cause of the higher prevalence of ioUS use in that group.

Based on our dataset, a few potential explanations exist for the fact that in our cohort resections with a neuro-anesthesiologist proved to be safer and more extensive.

First, the lower incidence of late complications in the NA-group may be the result of the higher extent of resection in subgroup 1 (neuro-anesthesiologist with dedicated oncological surgeon), which leads to an increased progression-free survival and consequently, less late

neurological deficits. A second explanation might be the psychological part of appointing a neuro-anesthesiologist to glioblastoma cases: working with an experienced neuro-anesthesiologist makes the surgeon more relaxed and focused, which consequently may have a notable impact on the surgeon's performance and outcomes. Multiple studies have pointed to the of interactive dynamics between surgical team members as key factors for surgical performance and patient outcomes.[17-19]

A third viable explanation might be the fact that the hemodynamics NA-led cases proved to be more strictly controlled. Our neuro-anesthesiologists prefer a slightly negative fluid balance (with adequate systematic hemodynamics), which could contribute to less brain edema and subsequent swelling of the brain, which in its turn leads to increased intraoperative field-of-vision and intracranial maneuverability for the surgeon. This results in increased intraoperative safety and decreased postoperative morbidity and could explain the lower incidence of the early postoperative complications predominantly in the NA-group.

Fourth, the higher incidence of late major postoperative complications in the GA group might (partially) be the result of the higher incidence of early major postoperative complications: early major and late major postoperative complications in the GA group were 28.8% and 26.9%, while this was 13.6% and 16.0% in the NA group. This is substantiated by the fact that more than half of the late postoperative deficits was permanent in the GA group (53.0%) while this was 30.4% in the NA group.

Limitations

The major limitation is the retrospective nature of this study. We expected a strong selection bias for patients operated under the supervision of a dedicated neuro-anesthesiologist. However, no significant differences in baseline characteristics were observed between groups, including well-known prognostic and predictive factors. Moreover, this study did only include GBM resections without mapping techniques, which might not be standard-of-care for some centers, especially for GBMs in or near eloquent areas. We therefore stress the importance of evaluating the benefit of the dedicated neuro-anesthesiologist in GBM resections with respect to (intraoperative) techniques for surgery in these areas.

To minimize most other possible bias correlated with the retrospective nature of this study, we underline the importance of a prognostic study to further investigate the potential of dedicated neuro-anesthesiologists in GBM surgery. These studies should also focus on the etiology behind the perceived lower incidence of postoperative deficits in GBM resections led by a neuro-anesthesiologist and the potential synergistic benefit of dedicated onco-neurosurgical teams. This study was conducted in a large high-volume university hospital with high-volume neurosurgeons (including experienced and specialized neuro-anesthesia

and neuro-oncological teams, which in itself is beneficial for patient outcomes); nevertheless, large university hospitals with a comparable study setting, patient selection and local procedures can expect a robustness in the external validity of our findings.

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CHAPTER 7

The SAFE-trial: Safe surgery for glioblastoma multiforme: awake craniotomy versus surgery under general anesthesia. Study protocol for a multicenter prospective randomized controlled trial

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ABSTRACT

Background

Surgery of GBM nowadays is usually performed under general anesthesia (GA) and resections are often not as aggressive as possible, due to the chance of seriously damaging the patient with a rather low life expectancy. A surgical technique optimizing resection of the tumor in eloquent areas but preventing neurological deficits is necessary to improve survival and quality of life in these patients. Awake craniotomy (AC) with the use of cortical and subcortical stimulation has been widely implemented for low-grade glioma resections (LGG), but not yet for GBM. AC has shown to increase resection percentage and preserve quality of life in LGG and could thus be of important value in GBM surgery.

Methods/Design

This study is a prospective, multicenter, randomized controlled trial (RCT). Consecutive patients with a glioblastoma in or near eloquent areas (Sawaya grading II/III) will be 1:1 randomized to awake craniotomy or craniotomy under general anesthesia. 246 patients will be included in neurosurgical centers in the Netherlands and Belgium. Primary end-points are: 1) Postoperative neurological morbidity and 2) Proportion of patients with gross-total resections. Secondary end-points are: 1) Health-related quality of life; 2) Progression-free survival (PFS); 3) Overall survival (OS) and 4) Frequency and severity of Serious Adverse Effects in each group. Also, a cost-benefit analysis will be performed. All patients will receive standard adjuvant treatment with concomitant chemoradiotherapy.

Discussion

This RCT should demonstrate whether AC is superior to craniotomy under GA on neurological morbidity, extent of resection and survival for glioblastoma resections in or near eloquent areas.

Trial registration

Clinicaltrials.gov: NCT03861299
Netherlands Trial Register (NTR): NL7589

BACKGROUND

Glioblastoma multiforme (GBM) or astrocytomas grade IV (WHO) are devastating tumors with one of the worst prognosis in oncology. The median survival after surgery and treatment with chemo and radiotherapy ranges from 12 to 15 months and no curative therapy is currently available [1,2]. The annual incidence is approximately 5 per 100,000 with a prevalence of 800-1000 cases each year in the Netherlands [3]. Patients usually present with speech difficulties, unilateral paresis in arms and/or legs, headache, cognitive problems or epilepsy [4]. Multiple studies show that extent of resection of the tumor improves survival in patients with GBM [5-8, 9-12]. Further analyses showed that patients who previously had complete resection derived the most benefit from the temozolomide regimen compared with those who had had incomplete resection [13]. Thus, in addition to the survival benefit associated with maximum cytoreductive surgery such surgery seems essential for the efficacy of modern adjuvant treatment.

More than 50% of GBMs are located near or in eloquent areas of the brain. Eloquent areas are important areas within the brain were speech and/or motor functions are located [4]. Damaging these areas during surgery has serious impact on the quality of life and could even exclude patients from after treatment with radio- and chemotherapy. The surgeon cannot identify these eloquent areas during resections under general anesthesia (GA). Therefore, when resecting GBMs in these areas, they are usually not operated as aggressive as possible, due the chance of seriously damaging the patient with a rather low life expectancy [1, 7, 9-12, 14]. However, partial or subtotal resections will benefit less from radio- and chemotherapy as total resections [5-8, 9-12]. A surgical technique optimizing resection of the tumor in eloquent areas but preventing neurological deficits is necessary to improve survival and maintain quality of life in these patients.

Awake craniotomy (AC) is the technique in which the patient is awake and cooperative during the resection of the tumor [14]. This allows the surgeon, together with cortical and subcortical mapping to prevent damage to eloquent cortical and subcortical areas during resection [15,16]. AC has shown to increase resection percentage and preserve quality of life in low-grade glioma (LGG) and could be of important value in the surgery of GBM [15, 17, 18]. Awake craniotomy could also optimize the extent of resection and therefore improve survival in these patients [15, 17-25]. Only very few studies have reported the use of AC in GBM [26, 27]. We recently showed in a meta-analysis and a retrospective matched case-control study that patients with GBM operated with AC had less early postoperative neurological morbidity and significantly higher percentage of total resection [28, 29]. AC could thus be of high value in the surgical treatment of GBM in eloquent areas. Therefore,

we designed the SAFE-trial: a multicenter randomized controlled study which will compare AC with craniotomy under GA in patients with GBM.

METHODS/DESIGN

Trial design

This is a prospective, multicenter, 2-arm randomized controlled trial (RCT). Eligible patients are randomized to AC (intervention arm) or craniotomy under GA (control arm).

Study objectives

The primary study objective is to assess the safety and efficacy of AC versus GA in patients with GBM in eloquent areas as expressed by NIHSS scores and extent of resection on MRI.

Secondary study objectives are to assess the postoperative quality of life and survival of AC versus GA as expressed by health-related quality of life (HRQoL, using the QLQ-C30, QLQ-BN20 and EQ-5D questionnaires) and (progression-free) survival (PFS/OS).

Study setting and participants

Patients will be recruited for the study from the neurosurgical or neurological outpatient clinic or through referral from general hospitals of the five participating neurosurgical hospitals. The four Dutch participating neurosurgical hospitals are Erasmus Medical Center (EMC) Rotterdam, Haaglanden Medical Center (HMC) The Hague, Elisabeth-Tweesteden Hospital (ETZ) Tilburg and University Medical Center Groningen (UMCG). The participating Belgian hospital is the University Hospital Gent (UZG). The study is open to additional participating neurosurgical centers. We expect to complete patient enrollment in 4 years. The estimated duration of the study (including follow-up) will be 5 years.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Age ≥18 years and ≤ 90 years
2. Tumor diagnosed as glioblastoma multiforme (GBM) on MRI with a distinct ring-like pattern of contrast enhancement with thick irregular walls and a core area reduced signal suggestive of tumour necrosis as assessed by the surgeon
3. Tumors situated in or near eloquent areas; motor cortex, sensory cortex, subcortical pyramidal tract or speech areas as indicated on MRI (Sawaya Grading II and II) [47]
4. The tumor is suitable for resection with both modalities (according to neurosurgeon)
5. Karnofsky performance scale 80 or more

6. Written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Tumors of the cerebellum, brain stem or midline
2. Multifocal contrast enhancing lesions
3. Substantial non-contrast enhancing tumor areas suggesting low grade gliomas with malignant transformation
4. Medical reasons precluding MRI (e.g. certain pacemakers)
5. Inability to give informed consent (e.g. severe language barrier)
6. Psychiatric history
7. Previous brain tumour surgery
8. Previous low-grade glioma.
9. Second primary malignancy within the past 5 years (with the exception of adequately treated in situ carcinoma of any organ or basal cell carcinoma of the skin).
10. Severe aphasia or dysphasia

Interventions

Craniotomy under general anaesthesia

On the evening before surgery 1.5–2.0 mg lorazepam is administered for anxiolysis.

60 min. before anaesthesia induction the patient receives 1g paracetamol p.o. and 7.5-15 mg midazolam p.o. if requested for sedation. 1g cefazoline is given iv. for antibiotic prophylaxis before anaesthesia induction.

General anaesthesia is induced intravenously with fentanyl 0.25-0.5 mg, propofol 100-200 mg and cis-atracurium 10-20 mg. After induction of anaesthesia, patient is orotracheally intubated and mechanical ventilation is applied. Respiratory rate and tidal volume are adjusted to keep the patient normocapnic.

An arterial line, central venous catheter (v. basilica), and urinary catheter are inserted. Anaesthesia is maintained with propofol (up to 10 mg/kg/h) and remifentanil (0.5-2 µg/kg/min). isoflurane (up to 1 MAC) and clonidine (1-2 µg/kg) may be added for maintenance, if necessary. The fluid management is aiming for normovolemia. 0.9% saline solution and balanced crystalloids are used for maintenance, in case of blood loss > 300 ml, HAES 130/0.4 solution will be given.

Temperature management is aiming for normothermia, warm-air blankets and warmed infusion lines are used. Arterial blood gas analysis is performed at the beginning of the procedure and repeated, if necessary. Electrolytes are controlled and substituted and hyperglycemia will be treated with insulin, if necessary.

The anesthetized patient is positioned on the table. Local infiltration of the scalp is performed with 20 ml lidocaine 1% with adrenaline 1:200.000 to reduce bleeding. The insertion points of the Mayfield clamp are not infiltrated with local anaesthetics.

Trephination and tumour resection are performed without any additional neuro-psychological monitoring, guided by STEALTH-neuronavigation. At the end of the procedure all anaesthetics are stopped and patient is brought to the Post Anaesthesia Care Unit (PACU). Detubation of the patient is performed as early as possible, if patient fulfils the detubation criteria (> 36 C body temperature, stable hemodynamics, sufficient spontaneous ventilation, adequate response to verbal orders). Postoperative analgesia is provided with Paracetamol i.v. or p.o. 1 g up to 4 dd and morphine 7.5 mg s.c. up to 4 dd, if necessary. At the PACU the patient is hemodynamically and neurologically monitored for 24 hours.

Awake craniotomy under local anaesthesia; procedure:
On the evening before surgery 1.5–2.0 mg lorazepam is administered for anxiolysis. Thirty minutes before anaesthesia induction an intramuscular injection of 7.5 mg piritramide and 25 mg promethazine is given. The patient is sedated with a bolus injection of propofol (0.5–1 $mg.kg^{-1}$) and kept sedated with a propofol infusion pump (mean: 4 $mg.kg^{-1}.h^{-1}$). An arterial line, central venous catheter, and urinary catheter are inserted. The patient is awakened and positioned on the table. At this point local anaesthesia for the fixation of the head in the Mayfield clamp and the surgical field is provided with a mixture of 10 mL lidocaine 2% with 10 mL bupivacaine 0.5% plus adrenaline 1:200,000 for the Mayfield clamp and up to 40 mL bupivacaine 0.375% with adrenaline 1:200,000 for the surgical field.

After positioning, clamp fixation, and surgical field infiltration, patients are sedated again for the trephination until the dura mater is opened, after local application of some drops of local anaesthetics. Propofol sedation is stopped after opening of the dura, with the patient awakening with as few external stimuli as possible. Cortical stimulation is performed with a bipolar electrical stimulator. The distance between both poles is 5 mm, and stimulation is performed by placing this bipolar pincet directly on the cortical surface and stimulating with increasing electrical biphasic currents of 2–12 mA (pulse frequency 60 Hz, single pulse phase duration of 100 microsec.) until motor or speech arrest is observed. For motor mapping a 2-second train and for speech mapping a 5-second train is used, respectively.

The Boston naming test and repetition of words is done in cooperation with a neuropsychologist/linguist, who will inform the neurosurgeon of any kind of speech arrest or dysarthria. The difference between these is not always clear, but can be distinguished from involuntary muscle contraction affecting speech. When localizing the motor and sensory cortex, the patient is asked to report any unintended movement or sensation in extremities or face.

Functional cortical areas are marked with a number. After completion of cortical mapping, a resection of the tumour is performed as radical as possible using an ultrasonic aspirator and suction tube, while sparing these functional areas. When the tumour margins or white matter is encountered or when on regular neuronavigation the eloquent white matter tracts are thought to be in close proximity, subcortical stimulation (biphasic currents of 8–16 mA, pulse frequency 60 Hz, single pulse phase duration of 100 microsec., 2-second train) is performed to localize functional tracts. If subcortical tracts are identified, resection is stopped. During the resection of the lesion close to an eloquent area, the patient is involved in a continuous dialogue with the neuropsychologist. That way the neurosurgeon has 'online'-control of these eloquent areas. In case of beginning disturbances of communication or of motor or sensory sensations the resection is cessated immediately. When, due to stimulation, an epileptic seizure occurs, this is stopped by administering some drops of iced saline on the just stimulated cortical area. Although not performed at our institution, continuous corticography may be used to monitor after discharge potentials to identify subclinical seizure activity. After resection of the tumour a final neurological examination is performed. During closure of the surgical field the patient is sedated with propofol again. After wound closure and dressing, sedation is stopped. The awake patient is transferred to the post-anaesthesia care unit, where the patient is hemodynamically and neurologically monitored for 24 hours.

***Intraoperative Imaging*:**
The use of fMRI, DTI (Diffusion Tensor Imaging), ultrasound or 5-ALA is allowed to be used in both groups on the surgeons indication.

Outcomes

Primary outcome measures
The primary outcomes are 1) the proportion of patients with ≥1 point deterioration on the NIHSS (National Institute of Health Stroke Scale) at 6 weeks postoperatively; and 2) the proportion of patients without residual contrast-enhancing tumour on the 48h postoperative MRI (≤0.175 cm^3 residual tumor).

Secondary outcome measures

The secondary outcomes are 1) health-realted quality of life (HRQoL) at 6 weeks, 3- and 6 months postoperatively (using the QLQ-C30, QLQ-BN20 and EQ-5D questionnaires); 2) progression-free survival (PFS) at 12 months defined as time from diagnosis to disease progression (occurrence of a new tumor lesions with a volume greater than 0.175 cm^3, or an increase in residual tumor volume of more than 25%) or death, whichever comes first; 3) overall survival (OS) at 12 months defined as time from diagnosis to death from any cause; 4) frequency and severity of (Serious) Adverse Events in each group (e.g. infections, intracerebral hemorrhage, epilepsy, aphasia and paresis/paralysis in extremities). Aphasia will be determined with a short neurolinguistic test-battery before and at 3 months after operation in each group including: Aphasia Bedside Check (ABC), shortened Token Test, verbal fluency (category and letter), picture description and the Montreal Cognitive Assessment (MOCA).

Randomization

Each participating center will randomize eligible and willing patients through the webbased clinical database and randomization application ALEA. The Clinical Trial Centre (CTC) of the Erasmus MC will build the randomization application by use of a dynamic allocation algorithm (minimization), in which patients are allocated to keep the imbalance between treatment groups to a minimum at every stage of recruitment within the covariates age (≤55 years *vs* >55years), Karnofsky performance scale (80–90 *vs* >90), and left or right hemisphere. Treatment allocation and allocated subject number will be shown immediately on screen and will in addition automatically be emailed to local investigators and other study personnel.

Study procedures: Clinical evaluations and follow up

1. Baseline

1) Assessment of baseline symptom(s) and medical history
2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D
4) Neurolinguistic test-battery (ABC, Shortened Token Test, verbal fluency, picture description, MOCA)

NIHSS – The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke, but has been used extensively for outcome in glioma surgery because of the lack of such scale for neuro-oncologic purposes and has been validated. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0

typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

QLQ-C30 – The European organisation for research and treatment of cancer (EORTC) developed the QLQ-C30 questionnaire for cancer patients, and the disease specific QLQ-BN20, specifically developed and validated for patients with brain tumor. Both tools have been tested and validated in clinical trials. The 50 questions in both questionnaires together take 20 minutes to complete.

The EORTC QLQ-C30 measures functioning scales - physical, role, emotional, cognitive and social; three symptom scales - fatigue, nausea/ vomiting and pain; six single item scales - dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact; and the overall HRQOL scale.

QLQ-BN20 – The EORTC QLQ-BN20 is designed for patients undergoing chemotherapy or radiotherapy and includes 20 items assessing visual disorders, motor dysfunction, communication deficit, various disease symptoms (e.g. headaches and seizures), treatment toxicities (e.g. hair loss), and future uncertainty. Both items are scaled, scored and transformed to a linear scale (0-100). Differences ≥10 points are classified as clinically meaningful changes in a HRQL parameter.)

EQ-5D – EQ-5D is a standardized instrument for measuring generic health status. The health status measured with EQ-5D is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life year (QALY) can be computed. QALYs gained is used as an outcome in cost-utility analysis which is a type of economic evaluation that compares the benefit and cost of health care programs or interventions

Aphasia Bedside Check (ABC) – ABC is a short screening test to detect aphasic disturbances at language comprehension and language production level at the main linguistic levels. It consists of 14 items in total. The cut-off score for signs of aphasia is ≤12.

Shortened Token Test – The shortened Token Test is a test for language comprehension and for the severity of a language disorder. The patient is asked to point and to manipulate geometric forms on verbal commands. It consists of 36 items. The cut-off score is 29.5.

Verbal fluency (category and letter) – Category and letter fluency are tests to assess flexibility of verbal semantic and phonological thought processing, semantic memory and concept generation. The patients is asked to produce words of a given category (animals, professions) or beginning with a given letter (D, A, T) within a limited time span.

Picture description – This is a subtest from the CAT-NL to assess semi-spontaneous speech in an oral and written way (5 minutes each condition). Scoring can be done according to the manual or more thoroughly according to the variables mentioned by Vandenborre et al.

Montreal Cognitive Assessment (MOCA) – The MOCA is a cognitive screening test to detect mild impairments across several cognitive domains; attention, verbal memory, language, visuo-constructive skills, conceptual thought, calculation and orientation. The total score is 30, the cut-off score is ≤26.

2. Preoperatively

1) MRI-brain-navigation with Gd-contrast (standard procedure)
2) Diffusion-tract imaging (DTI)

3. Postoperatively

1) MRI-brain with Gd-contrast within 48 hours postoperatively
   a. Extent of resection will be assessed by two independent neuroradiologists
2) Description of presenting symptom(s) at day 1-2-3- postoperatively
3) Full neurological examination at day 1-2-3 postoperatively

4. 6 weeks follow up after surgery

1) Description of presenting symptom(s)
2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D

5. 3 months follow up after surgery

1) Description of presenting symptom(s)
2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D
4) MRI-brain with Gd-contrast
5) Neurolinguistic test-battery (ABC, Shortened Token Test, verbal fluency, picture description, MOCA)

6. 6 months follow up after surgery

1) Description of presenting symptom(s)

2) Full neurological examination (NIHSS)
3) Questionnaires: EORTC QLQ-BN20, EORTC QLQ-C30 and EQ-5D
4) MRI-brain with Gd-contrast

7. 12 months follow up after surgery

1) Overall survival (as assessed by digital medical records of the hospital)
2) Progression-free survival (as assessed by routine MRI)

Sample size

This study has two primary endpoints. In order to guarantee that the overall type I error rate does not exceed 5%, we apply a weighted Bonferroni correction for multiple testing. The sample size calculations that follow take that into account.

For the first primary endpoint, proportion of patients with NIHSS deterioration at 6 weeks post-surgery, we assume a deterioration rate of 15% in the control group, and 3% in the experimental group. A two-sample test for proportions with continuity correction requires 222 patients (111 per arm) in total in order to detect the above mentioned difference of 12% with 80% power at a 4% significance level.

For the second primary endpoint, proportion of patients without residual contrast-enhancing tumor on postoperative MRI, we assume a success rate of 25% in the control group, and 50% in the experimental group [29]. A two-sample test for proportions with continuity correction requires 188 patients (94 per arm) in total in order to detect the above mentioned difference of 25% with 80% power at a 1% significance level.

In order to power the study for both primary endpoints, we should include the larger required number of patients, i.e. 222. A total of 222 eligible and evaluable patients allow the difference of 25% in proportion of patients without residual tumor to be detected with 88% power. Taking into account possible ineligibility and withdrawal of consent (we estimate this at 10%), a total of 246 patients will be included.

Data collection

All patient data is collected in the electronic data software ALEA (FormsVision B.V., Abcoude, The Netherlands). This software allows built-in logical checks and validations to promote data quality. Data entry is performed by the study coordinator or locally by trained research nurses and physicians.

Data analysis

All analyses will be according the intention to treat principle, restricted to eligible patients. That means that patients will be analysed according to the group they were randomized to, irrespective of the type of surgery actually received.

Patients initially registered but considered ineligible afterwards based on the histological analysis on tissue extracted during surgery, will be excluded from all analyses.

It is not expected that many patients will refuse AC after being randomized for this group. Yet these patients will not be excluded from the analyses, as suggested by the intention to treat principle. However, if this would have happened for some patients, a sensitivity analysis will be performed on the basis of the treatment actually received, i.e. per protocol analysis.

Primary study parameters

The primary endpoints will be analyzed using multivariate logistic regression, where treatment group effect will be corrected for minimization factors age group (≤55 years vs >55years), Karnofsky performance scale (80–90 vs >90), and left or right hemisphere (presented in order of decreasing prognostic value).

As the frequency of NIHSS deterioration is expected to be relatively low, we may not be able to correct for all randomization stratification factors as mentioned above. We will be including a stratification factor in the primary analysis model with each 10 observed events using the order of prognostic value as mentioned in the paragraph above, where the first 10 events will be used to estimate the effect of the arm. This rule will be applied in case less than 40 patients in total develop NIHSS deterioration.

In the so constructed multivariate logistic regression model the treatment arm effect will be tested at 4% significance level.

The primary analysis of proportion of patients without residual contrast-enhancing tumour consist of a multivariate logistic regression, where arm effect is corrected for all minimization factors. In this model the group effect will be tested at 1% significance level. Manual segmentation will be performed on axial T1 MRI contrast enhanced slices to measure tumor volume. A determination of volumes will be calculated blinded for the treatment group.

Secondary study parameters

Health related quality of life as measured with the QLQ-C30, QLQ-BN20, and EQ5D will be summarized cross-sectionally at 6 weeks, 3 and 6 months after surgery, as well as change from baseline. The difference between treatment arms will be described as well.

The Kaplan-Meier method will be used to estimate PFS and OS proportions per treatment group at appropriate time points, while the Greenwood estimate of the standard error will be used to construct the corresponding 95% CI. Multivariate Cox proportional hazards models will be build for PFS and OS where treatment group effect will be corrected for minization factors age group (≤55 years vs >55years), Karnofsky performance scale (80–90 vs >90), and left or right hemisphere. Additionally, competing risk analysis will be used to calculate cumulative incidence of PFS (with competing risks progression/relapse and death without progression/relapse which add up to 100% at every time point). SAE's in both groups will be described.

Study monitoring

The Clinical Trial Center of the Erasmus Medical Center will perform on-site monitoring visits to verify that the rights and well-being of patients are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). Monitoring visits will take place according to the study specific monitoring plan.

Adverse events (AEs) and serious adverse events (SAEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to neurosurgery. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded from start of surgery until 6 weeks after surgery. Serious adverse events are any untoward medical occurrence or effect that results in death; is life-threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgement by the investigator. An elective hospital admission will not be considered as a serious adverse event. Most of the (serious) adverse effects of treatments (awake surgery or surgery under generalised anaesthesia) will be mainly related to the surgery: post operative pain, nausea and anaemia (in case of massive blood loss), Infections, intracranial haemorrhage, epilepsy, aphasia, paresis/paralysis in arms or/and legs.

The neurological morbidity is under investigation in this trial and well known risk / complications of the craniotomy and can be attributed to the nature of the operation. Neurosurgical clinics are well adapted to prevent and treat such events. Therefore, the Local Investigator should report only Serious Adverse Events expedited (within 24h of first knowledge) that occur from start of surgery until 6 weeks after surgery and that result in death or are life threatening.

The sponsor will re-assess the expectedness and report fatal and life threatening SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge, followed by a period of maximum of 8 days to complete the initial preliminary report.

Publication of results

Trial results will be published in an international journal, communicated to neurological and neurosurgical associations and presented at (inter)national congresses.

DISCUSSION

Neurosurgeons have a daunting task: resecting the tumor with an extent as great as possible, while simultaneously minimizing the risk for postoperative complications and especially neurological morbidity. AC can significantly contribute to this goal by preserving the quality of life of these patients (and decreasing the risk of postoperative morbidity) when operating in eloquent areas, while increasing extent of resection (and maximizing postoperative survival).

With AC, the neurosurgeon uses electrocortical and subcortical mapping to differ eloquent brain tissue from brain- or tumor tissue that is safe to resect. To date, AC is used in particular for the resection of low-grade gliomas because of the usually near-eloquent location of these tumors and many studies have shown that AC greatly increases resection percentage while preserving QoL in low-grade glioma (LGG)[15,30]. Only very few studies have evaluated the use of these techniques in glioblastomas[15-18,26,27]. Arguably one of the more extensive studies was conducted by Sacko et al, who prospectively studied two groups of patients with supratentorial masses (n = 575), comparing AC with craniotomy under GA[18]. They found that using AC in glioma surgery proved to be superior to craniotomy under GA regarding neurological outcome and quality of resection ($p < 0.001$). Other substantial evidence came from the group of De Witt Hamer et al, who conducted an extensive meta-analysis including 8,091 adult patients who had surgery for supratentorial infiltrative glioma (high- and low-grade glioma), with or without intra-operative stimulation mapping (ISM; e.g. awake

craniotomy)[26]. They found that glioma resections using ISM were associated with fewer late major neurologic deficits and more extensive resection. However, the evidence from these studies is lacking the quality to substantiate the use of AC as standard treatment in glioblastoma surgery: the investigated groups are very small, mixed with II and –III tumors and lacking robust statistical analyses to correct for co-factors. Recently, more robust evidence regarding the use of AC in glioblastoma patients was published. Researchers from the Erasmus Medical Center conducted a retrospective matched case-control study including 148 patients undergoing craniotomy for glioblastoma[29]. They found that resection of glioblastoma using AC as associated with significantly greater extent of resection and less late minor postoperative complications as compared with craniotomy under GA without the use of surgery adjuncts. Moreover, a recent meta-analysis that specifically aimed to summarize the available research evidence on the use of AC in glioblastoma was conducted[28]. The analysis included 53 studies and 9,102 patients. This paper proved substantial evidence that AC yielded superior outcomes in glioblastoma resections as compared to GA: the overall postoperative median survival in the AC group was significantly longer (16.87 versus 12.04 months; $p<0.001$) and the postoperative complication rate was significantly lower (0.13 versus 0.21; $p<0.001$). Furthermore, extent of resection and preoperative patient KPS were indicated as prognostic factors, whereas patient KPS and involvement of eloquent areas were identified as predictive factors.

Overall, AC has been thoroughly demonstrated as an effective surgical technique in the current literature for low-grade glioma. AC is showing promising results as a technique used for glioblastoma resections, in particular in eloquent areas. Confirmation of these results is essential by means of RCTs.

Trial status

This trial started on April 1st, 2019. The study is open to additional participating neurosurgical centers.

DECLARATIONS

Acknowledgements

We would like to thank N. van der Velden-van der Meer for her support with the study design, -conduct and –monitoring and training of investigators. We also would like to thank the local investigators for their effort in conducting the study in the participating centers.

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Ethics approval and consent to participate

The study received approval by the Medical Ethics Committee (METC Zuid-West Holland) This trial has been registered in the Dutch Trial Register (NTR) and is conducted in compliance with the European Union Clinical Trials Directive (2001/20/EC) and the principles of the Declaration of Helsinki (2013).

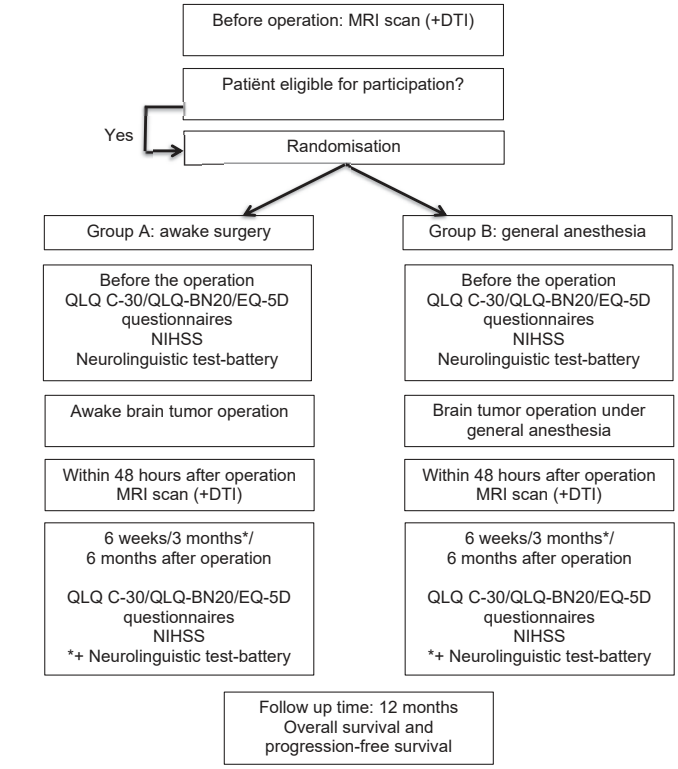

Figure 1: Study flowchart

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CHAPTER 8

Letter to the Editor:

Maximizing extent of resection while minimizing the risk of neurological morbidity in glioma patients: A novel grading scale to translate these surgical goals into a merged onco-functional clinical outcome

Jasper K.W. Gerritsen, Arnaud J.P.E. Vincent, Steven De Vleeschouwer

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Dear Editor,

We read with great interest the recent article by Wen *et al* reviewing the joint consensus by the SNO (Society for Neuro-Oncology) and EANO (European Society of Neuro-Oncology) on the current management and future directions for adult glioblastoma patients[1].

Dr. Wen and colleagues state in their chapter 'Surgical Management' that "the goal for glioblastoma surgery should be gross total resection of the enhancing solid tumor mass whenever feasible". They rightly stress that, in order to achieve this: "current standard surgical adjuncts include stereotactic navigation systems using anatomical and functional MRI datasets, intraoperative MRI, ultrasound, intraoperative functional monitoring and the fluorescent dye 5-aminolevulinic acid (5-ALA) to visualize vital tumor tissue, all of which are increasingly used to improve and maximize the extent of resection while reducing the risk of new neurological deficits." They conclude that "preventing new permanent neurological deficits is more important than maximizing the extent of resection, because glioblastomas are not cured by surgery alone, while recognizing and taking into consideration the benefits of maximal safe resection".

Neurosurgeons operating on glioblastomas in- or near eloquent areas face a well-known dilemma: maximizing extent of resection and -cytoreduction (to optimize progression-free- and -overall survival) while simultaneously minimizing the risk of postoperative neurological complications (to preserve clinical performance and -quality of life; QoL). These two goals do not exclude one another, but even reinforce each other though this may seem paradoxical at first[2]. As elaborately explained by Dr. Sanai and Prof. Berger[3], the answer lies mainly in the application of intraoperative stimulation mapping techniques – such as awake craniotomy, asleep mapping techniques (MEPs, SSEPs, continuous dynamic mapping) – or even DTI tractography or nTMS, for that matter.

Both the surgical-oncological objective (maximizing cytoreduction) and the goal to preserve neurological function (minimizing postoperative neurological morbidity) can be assessed and compared in both an objective and quantitative manner. The former usually as extent of resection (EoR) – defined as the percentage of (non)-contrast-enhancing tumor resected – the latter in terms of (a) QoL (using questionnaires such as the EQ-5D, QNQ-BN20 or QNQ-C30); (b) clinical performance (KPS, Karnofsky Performance Scale); or (c) neurological functioning (e.g. NIHSS, National Institute of Health Stroke Scale). All aforementioned outcome measures are very valid and useful, with the major advantage of being able to compare these outcomes between e.g. surgical modalities or centers.

However, there is currently no tool to assess these two goals simultaneously, consequently running the real risk of forgetting the actual intent of a monitored or unmonitored resection, which is optimizing the individual 'onco-functional' outcome. We deem the development of such a novel, integrated grading scale in regard to this vital outcome a necessary addition to the current arsenal of outcome measures in these patients. For example, the extent of resection can be combined with one of the 'functional' outcomes (e.g. KPS, NIHSS), thereby creating an individual twofold coordinate which represents a unique position of each single patient in an two-dimensional *(x,y)* graph. Alternatively, one can choose to incorporate both QoL *and* neurological morbidity in the model, subsequently creating a threefold coordinate with its associated representation in a corresponding three-dimensional *(x,y,z)* graph. Different subgroups of glioblastoma patients will consequently yield a cluster of co-ordinates, thereby enabling researchers to compare subgroups more effectively and in better alignment with the original aim of (monitored) resection. We believe that, by reflecting the existing surgical dilemma in a novel clinical outcome measurement, this 'onco-functional' outcome-coordinate has the potential to be of great additional value as it really captures the relevant outcome parameters to assess the maximal, safe resection for each individual, single patient. This will ultimately allow us to compare outcome-coordinates for different surgical strategies in comparable subgroups of glioma patients.

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Steven De Vleeschouwer, MD PhD

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CHAPTER 9

A novel postoperative onco-functional outcome (OFO) grading scale to assess extent of resection and postoperative neurological morbidity or KPS simultaneously to compare surgical outcomes in glioblastoma subgroups

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**shared last authorship*

Under review (Neuro-Oncology)

ABSTRACT

Background

Glioblastoma resections in or near eloquent areas are challenging since neurosurgeons strive to maximize extent of resection and minimize postoperative neurological deficits. There is currently no tool to assess these two goals in glioblastoma patients simultaneously. We aimed to develop a new onco-functional outcome (OFO) that merges these outcomes to create an objective tool for neurosurgeons to help with surgical decision making.

Methods

848 patients with tumor resection for primary eloquent glioblastoma between January 2010 and October 2020 at three large university medical centers from the Netherlands and Belgium were included from an initial cohort of 2691 glioblastoma patients. Cluster analyses were used to divide the patients into different OFO subgroups based on either the combination (1) extent of resection and difference in post-op vs. pre-op neurological score (ΔNIHSS) or (2) extent of resection and difference in post-op vs. pre-op Karnofsky Performance Score (ΔKPS). Both models were tested at 6 weeks and 6 months postoperatively. Furthermore, survival outcomes for OFO subgroups were analyzed.

Results

Patient clustering with the ΔNIHSS-EOR and ΔKPS-EOR models yielded 5 distinct OFO subgroups: OFO 1a, OFO 1b, OFO 2, OFO 3a and OFO 3b. Subgroups varied significantly in terms of preoperative KPS, NIHSS and ASA scores, use of mapping and surgical adjuncts, adjuvant therapy, postoperative tumor volume, extent of resection, ΔNIHSS and ΔKPS. Survival analyses demonstrated that overall survival and progression free survival differed significantly between subgroups.

Conclusions

This study establishes a proof-of-concept of the development of a novel onco-functional outcome scale in glioblastoma patients. The presented OFO scale combines extent of tumor resection with the post-op/pre-op difference in neurological morbidity (ΔNIHSS) or overall functioning (ΔKPS). The ΔNIHSS-EOR model is better than the ΔKPS-EOR model at distinguishing between the OFO subgroups. Moreover, the ΔNIHSS-EOR model at 6 weeks proved to be best for comparing OFO subgroups based on postoperative morbidity and EOR, while the ΔNIHSS-EOR model at 6 months postoperatively yielded the best results for comparing survival outcomes. The presented OFO scale can be used in a clinical setting to help with surgical decision making and in a scientific setting to compare glioblastoma patient subgroups more effectively.

INTRODUCTION

Glioblastoma resections in or near eloquent areas are challenging since neurosurgeons strive to maximize extent of resection while minimizing postoperative neurological deficits.

The former can be seen as an oncological objective: to resect as much of the tumor as possible to obtain maximal cytoreduction; the latter as a functional objective: to decrease the risk of postoperative worsening – either expressed as neurological morbidity or reduced quality of life.

These two surgical objectives can be assessed and compared in both an objective and quantitative manner. The oncological objective is usually assessed as extent of resection (EOR) or alternatively, residual tumor volume. The functional objective can be measured with the help of questionnaires that objectify the patient's quality of life (e.g. EORTC QLQ-BN20, QLQ-C30) [1,2], or with widely used standardized scales that represent either the patient's clinical performance (Karnofsky Performance Scale, KPS) or neurological functioning (e.g. National Institute of Health Stroke Scale, NIHSS) [3].

These tools allow neurosurgeons to measure how well one of these objectives have been met for individual patients (clinical setting) and cohorts of patients (scientific setting).

However, there is currently no tool available to assess these two objectives in patients simultaneously. This matters, since comparing patients or patient cohorts with extent of resection (or residual volume) and quality of life/neurological morbidity as two separate entities fails to adequately address the true purpose of glioblastoma resections: to optimize the "onco-functional outcome" in these patients. The development and addition of a new grading scale that merges these two objectives is therefore vital to help comparing these patients more effectively. One way to establish this merge is to introduce a coordinate for each patient in a two-dimensional *x,y* graph with a quantitative measurement of the oncological objective on one axis and the functional objective on the other. This would lead to the presentation of different subgroups of glioblastoma patients as a cluster of coordinates [4].

We aimed to develop this new "onco-functional outcome" (OFO) with two main purposes in mind. First, this new grading scale would have to be able to compare different glioblastoma patients on an individual level and a group-level. This would mean that the different OFO groups would have to represent clinically distinct glioblastoma subgroups with potentially different "third" outcomes (e.g. overall and/or progression-free survival). Second, the new OFO scale would have to be both easy and practical to use in a clinical and scientific setting.

METHODS

This retrospective study using prospectively collected data was performed in an international multicenter setting. The study was approved by the ethics committee of all three centers and adhered to the STROBE reporting guidelines. 2691 patients with glioblastoma surgery between January 2010 and October 2020 at the Erasmus Medical Center (Rotterdam, The Netherlands), Haaglanden Medical Center (The Hague, The Netherlands) and University Hospital Leuven (Leuven, Belgium) were screened for eligibility. 848 patients with tumor resection for primary, eloquent glioblastoma were eligible for inclusion in the analysis subsets. Subsequently, 748 patients were included in the subset at 6 weeks postoperatively, and 575 patients in the subset at 6 months postoperatively (Figure 1). Additional details on data collection are given in the eMethods section of the Data Supplement. For both timepoints, two OFO models were developed: based on either ΔNIHSS-EOR or ΔKPS-EOR. ΔNIHSS and ΔKPS were based on the difference in postoperative NIHSS or KPS score (at 6 weeks or 6 months postoperatively) in comparison with the preoperative score.

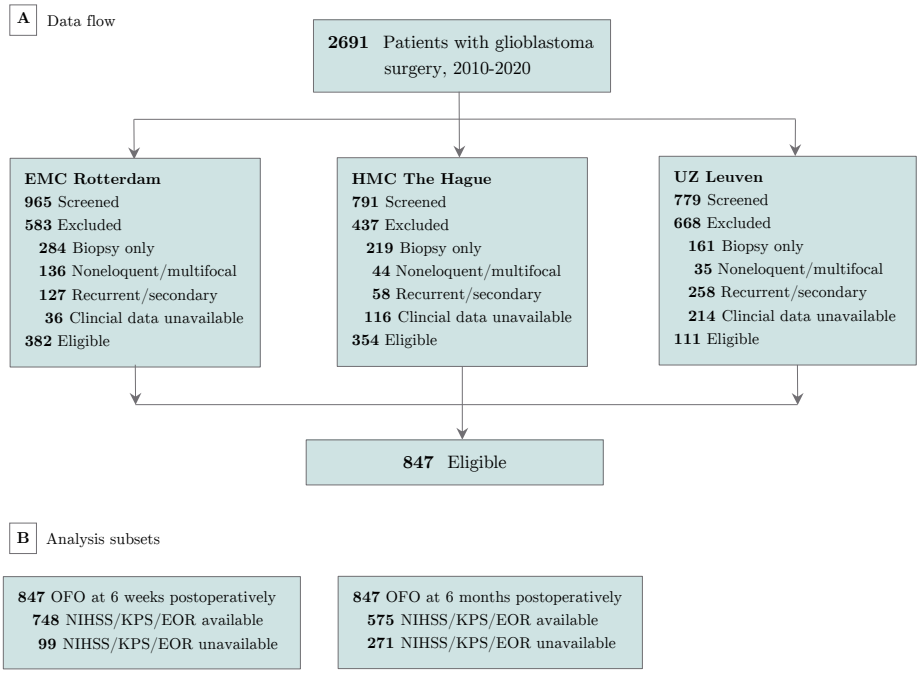

Figure 1: Data Flow Diagram

Statistical analysis

All analyses were performed using *R* (version 4.1.0, R Institute for Statistical Computing, Vienna, Austria). Demographic cohort data were summarized using standard descriptive statistics. To test for differences in categorical variables, the Pearson's χ^2 test was used. For numerical variables (>2 groups), the one-way ANOVA test was performed. Cluster analyses were performed with an unsupervised machine learning model (*ggplot2*, *ggpubr* and *factoextra* packages in *R*). For vector quantization, *k*-means clustering with Euclidean distances to minimize the within-cluster sum of squares was used with the Lloyd's algorithm. For each onco-functional outcome measurement, the most appropriate number of clusters was identified with the Elbow method (eFigure 1, Data Supplement). Survival analyses were performed with plotted Kaplan-Meier (KM) curves for overall survival (OS) and progression-free survival (PFS) (*survival*, *survminer* and *dplyr* packages in *R*). OS and PFS were analyzed for all [OFO subgroups] of both OFO models at 6 weeks and 6 months postoperatively. Overall survival was defined as the date of tumor resection until death or last follow up. Statistical significance between the survival times of different OFO subgroups was tested with the log-rank test. The alpha for statistical significance was set at 5% for all tests.

RESULTS

OFO subsets: 6 weeks and 6 months postoperatively

Of the 748 patients included in the OFO 6 weeks subset, 461 (61.6%) were male and 247 (38.4%) were female (Table 1); median age at diagnosis was 61.7 (IQR 54.0-70.0). Median preoperative KPS was 80 (IQR 80-90), median preoperative ASA score was 2 (IQR 2-2) and preoperative NIHSS score was 1 (IQR 0-2). Of the 478 patients with known *IDH*-status, 448 patients had *IDH*-wildtype tumors (93.7%); of the 597 patients with MGMT status measured, 250 had methylated MGMT tumors (41.9%). One hundred and eighteen (15.8%) tumors were resected with the help of intraoperative electrophysiological mapping (e.g. awake craniotomy), 96 (12.8%) tumors with intraoperative ultrasound and 50 (6.7%) tumors with intraoperative fluorescence. Moreover, 645 (86.3%) patients received adjuvant chemotherapy and radiotherapy. Mean preoperative contrast-enhancing (CE) tumor volume in this group was 63.8% (SD=54.3); mean postoperative CE tumor volume was 5.9 ml (SD=11.7) with a mean extent of resection of 91.4% (SD=13.1). Overall median progression-free survival (PFS) of these patients was 9.0 months (IQR 4.0-18.0) and median overall survival of 15.0 months (IQR 9.0-28.0 months). In general, patient characteristics of the 6 months subset were comparable with the 6 weeks subset (Table 1). However, all patients in this subset (n = 575, 100%) received adjuvant treatment with chemotherapy and radiotherapy, which resulted in a higher median PFS (11.0 months, IQR 6.0-21.0) and median OS (18.5 months, IQR 12.0-33.3) than the 6 weeks subset.

Table 1: Patient characteristics

Characteristic	OFO 6 weeks subset (n = 748)	OFO 6 months subset (n = 575)
Gender		
Male	461/748 (61.6)	369/575 (64.2)
Female	287/748 (38.4)	206/576 (35.8)
Age at diagnosis, years		
Mean (SD)	61.7 (10.8)	60.3 (11.1)
Median (IQR)	63.0 (54.0-70.0)	61.0 (54.0-68.0)
Range	22.0-85.0	22.0-79.0
Preoperative KPS		
<60	10/748 (1.3)	5/575 (0.9)
60	31/748 (4.1)	17/576 (3.0)
70	104/748 (13.9)	63/575 (11.0)
80	221/748 (29.5)	167/575 (29.0)
90	281/748 (37.6)	233/575 (40.5)
100	101/748 (13.5)	90/575 (15.7)
Median preoperative KPS (IQR)	80 (80-90)	90 (80-90)
Preoperative ASA score		
I	98/734 (13.4)	88/562 (15.7)
II	464/734 (63.2)	350/562 (62.3)
III	165/734 (22.4)	118/562 (21.0)
IV	7/734 (1.0)	6/562 (1.1)
Median preoperative ASA score (IQR)	2 (2-2)	2 (2-2)
Preoperative NIHSS score		
0	269/748 (36.0)	225/575 (39.1)
1	219/748 (29.3)	163/575 (28.7)
2	141/748 (18.9)	98/575 (17.0)
3	54/748 (7.2)	42/575 (7.3)
4	27/748 (3.6)	18/575 (3.1)
>4	38/748 (5.1)	29/575 (5.0)
Median preoperative NIHSS score (IQR)	1 (0-2)	1 (0-2)
Tumor location by lobe		
Frontal	244/748 (32.6)	179/575 (31.1)
Parietal	186/748 (24.9)	148/575 (25.7)
Temporal	258/748 (34.5)	206/575 (35.8)
Occipital	60/748 (8.0)	42/575 (7.3)
Tumor location by hemisphere		
Left	420/748 (56.1)	337/575 (58.6)
Right	328/748 (43.9)	238/575 (41.4)
IDH status		
Wildtype	448/478 (93.7)	358/379 (94.5)
Mutant	30/478 (6.3)	21/379 (5.5)

Table 1: Patient characteristics (Continued)

Characteristic	OFO 6 weeks subset (n = 748)	OFO 6 months subset (n = 575)
MGMT status		
Methylated	250/597 (41.9)	149/364 (40.9)
Unmethylated	348/597 (58.3)	215/364 (59.1)
Mapping and surgical adjuncts		
Intraoperative electrophysiological mapping	118/748 (15.8)	87/575 (15.1)
Intraoperative ultrasound	96/748 (12.8)	72/575 (12.5)
Intraoperative fluorescence	50/748 (6.7)	102/575 (17.7)
Postoperative adjuvant therapy		
Radiotherapy only	51/747 (6.8)	0/575 (0.0)
Chemotherapy only	11/747 (1.5)	0/575 (0.0)
Both	645/747 (86.3)	575/575 (100.0)
None	40/747 (5.4)	0/575 (0.0)
Preoperative CE tumor volume, ml		
Mean (SD)	63.8 (54.3)	60.4 (50.0)
Median (Q1-Q3)	49.7 (25.0-88.6)	47.3 (23.5-85.0)
Range	0.4-237.0	0.4-212.0
Postoperative CE tumor volume, ml		
Mean (SD)	5.9 (11.7)	5.1 (11.2)
Median (Q1-Q3)	1.6 (0-5.8)	1.3 (0-4.7)
Range	0.0-94.6	0.0-94.0
Extent of resection CE tumor, % by volume		
Mean (SD)	91.4 (13.1)	92.5 (12.1)
Median (Q1-Q3)	96.7 (88.3-100.0)	97.6 (89.6-100.0)
Range	8.9-100.0	8.9-100.0
Median progression-free survival, months (IQR)	9.0 (4.0-18.0)	11.0 (6.0-21.0)
Median overall survival, months (IQR)	15.0 (9.0-28.0)	18.5 (12.0-33.3)

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing.

Patient characteristics for the three patient cohorts (Erasmus MC, n = 382; Haaglanden MC, n = 354; UZ Leuven, n = 111) are summarized in the Data Supplement (eTable 1). Overall, these cohorts were comparable for patient, tumor, clinical and imaging related data. Though, the median PFS and OS differed slightly between cohorts, potentially due to differences in postoperative adjuvant therapy and/or use of mapping and surgical adjuncts. Median PFS was 6.0 months (IQR 3.0-10.0) for the EMC cohort, 12.0 months (IQR 4.0-25.5) for the HMC cohort and 10.5 months (6.0-17.5) for the UZL cohort. Median OS was 11.0 months (IQR 6.0-17.9) vs. 15.5 months (IQR 5.5-28.0) vs. 16.0 months. (IQR 11.0-23.5) respectively.

	Preoperative NIHSS/KPS status	Surgical approach	Postoperative NIHSS/KPS status	Postoperative survival
OFO 1a	Significant impairment	Aggressive with mapping or adjuncts	Improved	Excellent
OFO 1b	No or minimal impairment	Aggressive with mapping or adjuncts	Preserved	Excellent
OFO 2	No or minimal impairment	Defensive	Preserved	Good
OFO 3a	No or minimal impairment	Defensive	Preserved	Moderate
OFO 3b	No or minimal impairment	Aggressive with mapping or adjuncts	Decreased	Moderate

Figure 2a: Clustering of OFO subgroups – General interpretation

General interpretation of the OFO grading system

Patients were clustered at two timepoints (6 weeks and 6 months postoperatively) using two OFO models (ΔNIHSS-EOR and ΔKPS-EOR). Note that a positive ΔNIHSS indicates postoperative neurological worsening and that a positive ΔKPS indicates postoperative improvement in patient functioning. Clustering divided the total patient cohort in 5 groups at both timepoints: OFO 1a, OFO 1b, OFO 2, OFO 3a and OFO 3b (Figure 2a and 2b, Data Supplement [eTable 2, eTable 3, eTable 4]). OFO subgroups differed from each other most notably with regard to preoperative KPS, preoperative NIHSS score, percentage of resections with the use of intraoperative mapping or fluorescence, adjuvant therapy, tumor volumetrics, postoperative NIHSS score, ΔNIHSS, ΔKPS, PFS and OS. Kaplan-Meier curves were plotted for OS and PFS for both OFO models at 6 weeks (Figure 3) and 6 months postoperatively (Figure 4).

OFO 1a and OFO 1b correspond to the subgroups of patients with an improvement in KPS or NIHSS score (OFO 1a), or a KPS or NIHSS score that remained the same postoperatively [as preoperatively] (OFO 1b) and a high EOR. OFO 2 and OFO 3a also include patients with comparable KPS or NIHSS scores postoperatively vs. preoperatively, but the EOR in these subgroups is moderate (OFO 2) to low (OFO 3a) in comparison with subgroups OFO 1a and OFO 1b. Last, OFO 3b corresponds to the subgroup of patients with a worsened KPS or NIHSS score postoperatively (6 weeks and 6 months) in comparison with the preoperative score and a high EOR.

ΔNIHSS-EOR model at 6 weeks postoperatively

A high percentage of resections in subgroups OFO 1a (n = 72) and OFO 1b (n = 466) was done with intraoperative mapping (OFO 1a: 13.9%; OFO 1b: 20.2%) or intraoperative fluorescence (OFO 1a: 27.8%; OFO 1b: 19.3%). A large proportion received adjuvant chemotherapy and radiotherapy (OFO 1a: 95.8%; OFO 1b: 90.1%). OFO 1a had the highest preoperative NIHSS score of all subgroups (median 3, IQR 2-5). Median ΔNIHSS for these subgroup was -3 (OFO 1a) and 0 (OFO 1b); median extent of resection was 97.5% (IQR 93.3-99.9) in OFO 1a and 97.8% (IQR 93.3-100.0) in OFO 1b; median PFS was 7.8 months

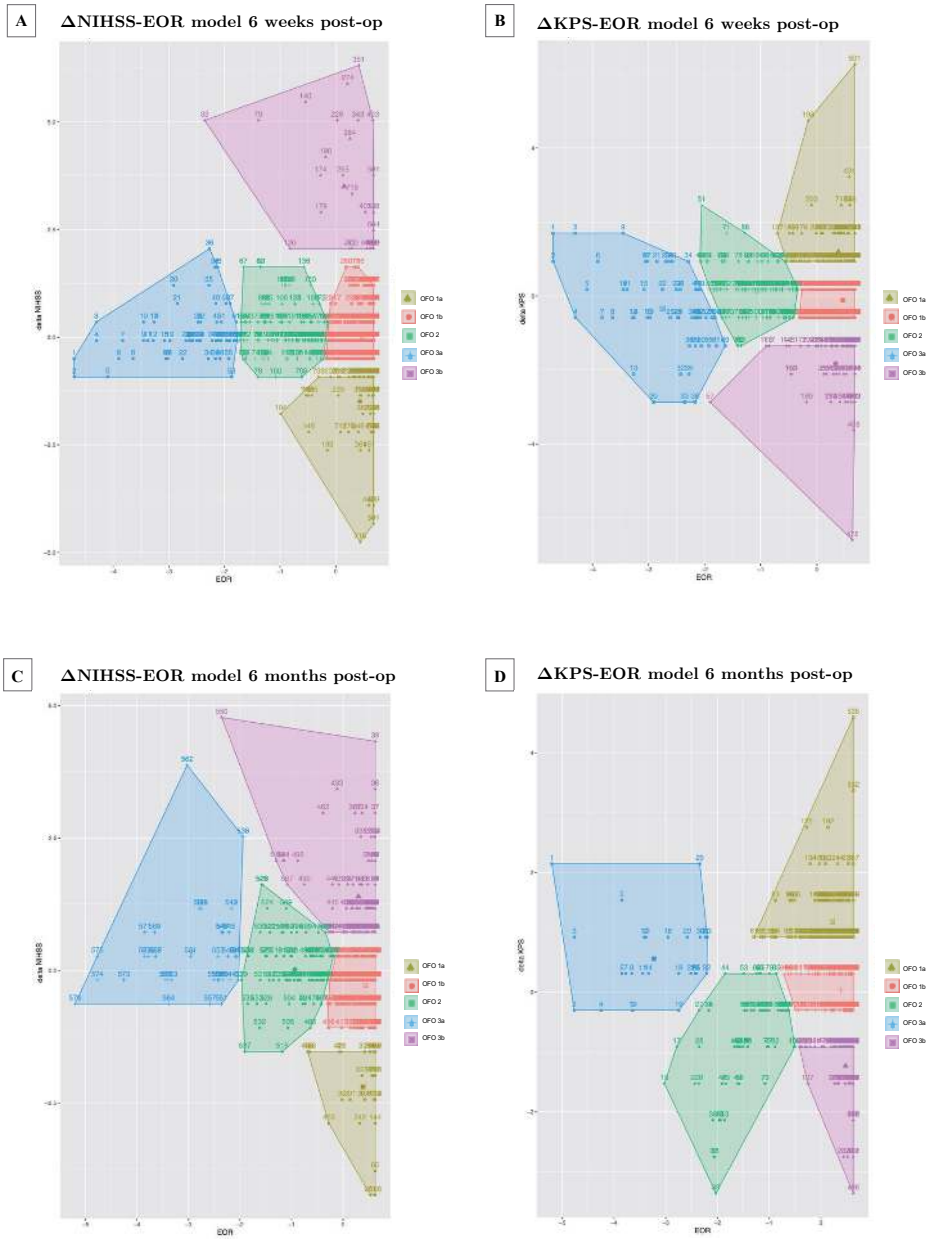

Figure 2b: Clustering of OFO subgroups at 6 weeks and 6 months postoperatively

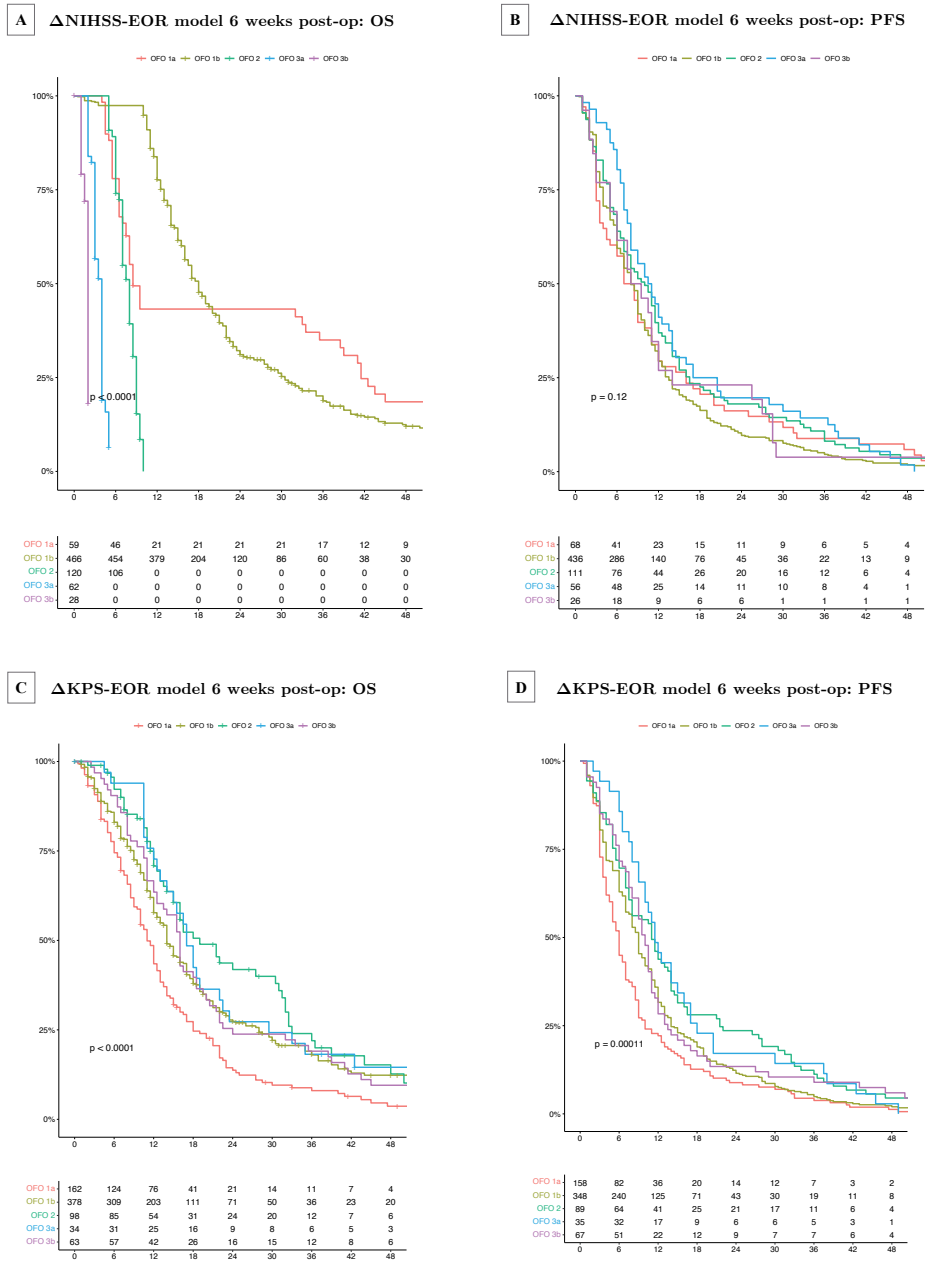

Figure 3: Kaplan-Meier curves for Overall Survival and Progression-Free Survival for OFO subgroups of ΔNIHSS-EOR and ΔKPS-EOR models at 6 weeks postoperatively

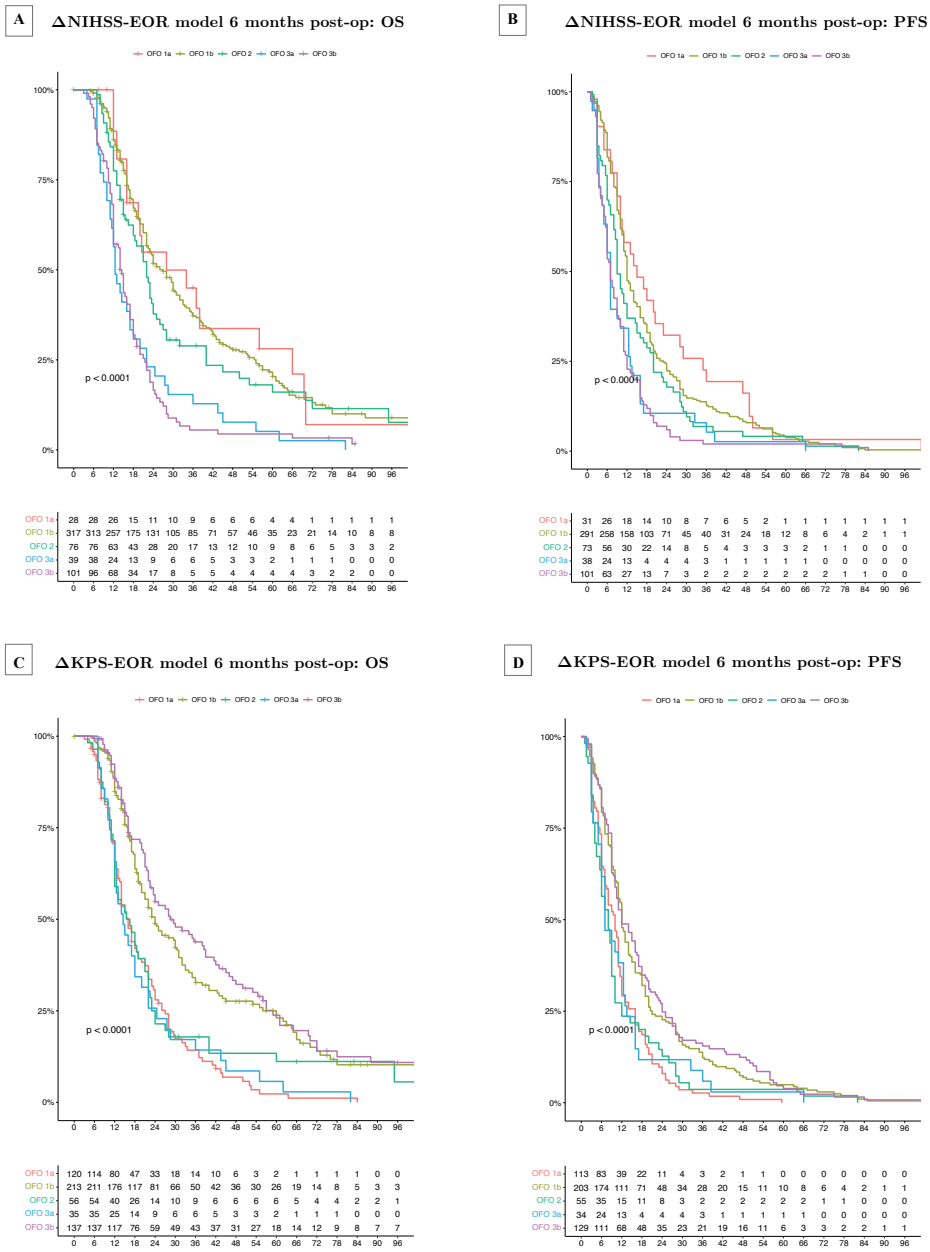

Figure 4: Kaplan-Meier curves for Overall Survival and Progression-Free Survival for OFO subgroups of ΔNIHSS-EOR and ΔKPS-EOR models at 6 months postoperatively

(IQR 6.0-11.0) in OFO 1a and 8.0 months (IQR 7.0-9.0) in OFO 1b; median OS was 8.5 months (IQR 8.0-38.5) in OFO 1a and 18.0 months (IQR 17.0-19.0) in OFO 1b.

Patients in subgroups OFO 2 (n = 120) and OFO 3a (n = 62) had comparable scores for preoperative KPS, ASA and NIHSS as subgroup OFO 1b. However, the proportion of resections done with intraoperative mapping (4.2% in OFO 2, 0.0% in OFO 3a) or intraoperative fluorescence (8.3% in OFO 2, 6.5% in OFO 3a) were considerably lower than in subgroups OFO 1a and OFO 1b. Furthermore, median EOR was significantly lower in these subgroups: respectively 74.4% (IQR 65.3-79.8) and 43.2 (IQR 65.3-79.8%) and a lower proportion of patients received both adjuvant chemotherapy and radiotherapy (79.2% in OFO 2, 72.6% in OFO 3a). Median ΔNIHSS for these subgroups was 0 (IQR 0-1); median PFS was 8.0 months (IQR 7.0-8.0) in OFO 2 and 4.0 months (IQR 3.0-4.0) in OFO 3a; median OS was 10.0 months (IQR 7.5-11.5) in OFO 2 and 10.8 months (IQR 8.0-14.0) in OFO 3a.

Patients in subgroup OFO 3b (n = 28) were similar regarding KPS, and NIHSS and ASA scores to subgroups 1b, 2 and 3a. Like in subgroup 1b, a high proportion of resections was done with intraoperative mapping (14.3%) or intraoperative fluorescence (25.0%) and the median extent of resection was 92.9% (IQR 84.2-98.8). However, their median postoperative NIHSS score was the worst of all subgroups (9.5, IQR 6-12), as was their median postoperative ΔNIHSS (7.5, IQR 5-12), and their median OS (8.8 months, IQR 6.0-14.0). Notably, median PFS did not differ significantly from other subgroups (.0 months, IQR 2.0-2.0, p = 0.12).

ΔKPS-EOR model at 6 weeks postoperatively

A low percentage of resections in subgroup OFO 1a (n = 162) was done with intraoperative mapping (4.3%) or intraoperative fluorescence (6.2%), which was in contrast with OFO 1a subgroup of the ΔNIHSS-EOR model. Also, a lower proportion received adjuvant chemotherapy and radiotherapy (74.1%). OFO 1a also had the lowest preoperative KPS score of all subgroups (median 80, IQR 70-90). Median ΔKPS for this subgroup was 10 (IQR 10-10); median extent of resection was 95.7 % (IQR 88.9-99.5); median PFS was 6.0 months (IQR 5.0-7.0), and median OS was 1.0 months (10.0-12.5).

Patients in subgroup OFO 1b (n = 378) had preoperative KPS, ASA and NIHSS scores that were comparable with OFO 1a. However, in this subgroup a higher percentage of resections was done with intraoperative mapping (17.2%) or ultrasound (18.5%), and a larger proportion received adjuvant chemotherapy and radiotherapy (87.8%). Median ΔKPS for this subgroup was 0 (IQR -10/0); median extent of resection was 97.6% (IQR 92.1-100.0); median PFS was 9.0 months (IQR 8.0-9.5), and median OS was 14.0 months (IQR 13.0-16.0).

Patients in subgroups OFO 2 (n = 98) and OFO 3a (n = 40) had preoperative KPS that were comparable with subgroup OFO 1b. Though, preoperative ASA and NIHSS scores were slightly higher in subgroup 3a (median ASA 2, IQR 2-3; median NIHSS score 1; IQR 0-3). The proportion of resections done with intraoperative mapping (17.3% in OFO 2, 27.5% in OFO 3a) or intraoperative fluorescence (6.1% in OFO 2, 60.0% in OFO 3a) were comparable or higher than in subgroups OFO 1a and OFO 1b. However, median EOR was significantly lower in subgroups OFO 2 and OFO 3a: respectively 64.4% (IQR 54.8-71.9) and 43.2% (IQR 25.4-49.0) even though a higher proportion of patients received both adjuvant chemotherapy and radiotherapy (96.9% in OFO 2, 97.5% in OFO 3a). Median ΔKPS for these subgroups was 0 (IQR 0-1); median PFS was 11.0 months (IQR 8.0-14.0) in OFO 2 and 11.5 months (IQR 10.0-14.0) in OFO 3a; median OS was 19.0 months (IQR 16.0-31.5) in OFO 2 and 16.0 months (IQR 12.5-19.5) in OFO 3a.

Preoperative ASA scores of patients in subgroup OFO 3b (n = 70) were similar to subgroups 1a, 1b, 2 and 3a, but had a slightly higher preoperative median NIHSS score (2, IQR 1-3) and higher preoperative median KPS score (90, IQR 80-90). Like in subgroups 1b, 2 and 3a, a high proportion of resections was done with intraoperative mapping (25.7%) or intraoperative fluorescence (100%). The median EOR in this subgroup was 97.3% (IQR 92.3-100.0). However, their median postoperative KPS score was the worst of all subgroups (70, IQR 50-70), as was their median postoperative ΔKPS (-20, IQR -20/-30), and their median OS (16.0 months, IQR 12.5-19.5). Notably, median PFS did not differ significantly from subgroups 1b, 2 and 3a (10.0 months, IQR 9.0-11.0).

ΔNIHSS-EOR model at 6 months postoperatively

A high percentage of resections in subgroups OFO 1a (n = 32) and OFO 1b (n = 325) was done with intraoperative mapping (OFO 1b: 25.6%) or intraoperative fluorescence (OFO 1a: 37.5%; OFO 1b: 31.1%). Similar to the 6 weeks model, OFO 1a had the highest preoperative NIHSS score of all subgroups (median 4, IQR 4-6). Median ΔNIHSS for these subgroup was -4 (OFO 1a) and 0 (OFO 1b); median extent of resection was 99.0% (IQR 95.5-100.0) in OFO 1a and 98.7% (IQR 94.4-100.0) in OFO 1b; median PFS was 15.0 (IQR 10.0-29.0) in OFO 1a and 12.0 months (IQR 11.5014.0) in OFO 1b; median OS was 28.0 months (IQR 19.5-69.5) in OFO 1a and 27.0 months (IQR 23.0-31.0) in OFO 1b.

Patients in the subgroups OFO 2 (n = 76) and OFO 3a (n = 39) had comparable scores for ASA and NIHSS as subgroup OFO 1b. Though, median preoperative KPS score was slightly lower in OFO 3a (80, IQR 80-90). The proportion of resections done with intraoperative mapping (7.9% in OFO 2, 0.0% in OFO 3a) or intraoperative fluorescence (6.6% in OFO 2, 12.8% in OFO 3a) were considerably lower than in subgroups OFO 1a and OFO 1b. Furthermore, median EOR was significantly lower in these subgroups: respectively 74.6%

(IQR 67.3-80.7) and 45.8 (IQR 29.6-50.9). Median ΔNIHSS for these subgroups were 1 (IQR 0-3) in OFO 2 and 2 (IQR 1-3) in OFO 3a; median PFS was 9.0 months (IQR 8.5-12.0) in OFO 2 and 7.0 months (IQR 5.0-12.5) in OFO 3a; median OS was 22.0 months (IQR 18.0-25.0) in OFO 2 and 12.5 months (IQR 11.5-18.0) in OFO 3a.

Patients in subgroup OFO 3b (n = 104) were similar regarding KPS, and NIHSS and ASA scores to subgroups 1b, 2 and 3a. Like in subgroup 1b, a high proportion of resections was done with intraoperative mapping (14.3%) or intraoperative fluorescence (13.5%) and the median extent of resection was 98.0% (IQR 92.7-100.0). However, their median postoperative NIHSS score was the worst of all subgroups (4, IQR 3-5), as was their median postoperative ΔNIHSS (3, IQR 2-4). Median OS (14.0 months, IQR 12.0-17.0) and PFS (7.0 months, IQR 6.0-9.0) were comparable to OFO 3a.

ΔKPS-EOR model at 6 months postoperatively

A high percentage of resections in subgroups OFO 1a (n = 147) and OFO 1b (n = 221) was done with intraoperative mapping (OFO 1a: 12.9%; OFO 1b: 24.4%), intraoperative ultrasound (OFO 1a: 17.7%; OFO 1b: 11.8%) or intraoperative fluorescence (OFO 1a: 16.3%; OFO 1b: 21.2%). OFO 1a had the highest preoperative NIHSS score of all subgroups (median 2, IQR 1-3) and worst KPS of all subgroups (median 80, IQR 70-80). Median ΔKPS for these subgroup was 10 (OFO 1a) and 0 (OFO 1b); median extent of resection was 95.5% (IQR 89.3-99.2) in OFO 1a and 98.9% (IQR 93.3-100.0) in OFO 1b; median PFS was 10.0 months (IQR 7.5-11.0) in OFO 1a and 12.0 months (IQR 11.0-14.0) in OFO 1b; median OS was 16.0 months (IQR 14.0-19.0) in OFO 1a and 24.0 months (IQR 21.0-35.0) in OFO 1b.

Patients in subgroups OFO 2 (n = 62) and OFO 3a (n = 27) had comparable scores for preoperative KPS, ASA and NIHSS as subgroup OFO 1b. However, the proportion of resections done with intraoperative mapping (3.2% in OFO 2, 0.0% in OFO 3a), intraoperative ultrasound (8.1% in OFO 2; 0.0% in OFO 3a) or intraoperative fluorescence (9.7% in OFO 2, 7.4% in OFO 3a) were considerably lower than in subgroups OFO 1a and OFO 1b. Furthermore, median EOR was significantly lower in these subgroups: respectively 66.1% (IQR 58.1-72.3) and 33.1% (IQR 26.7-48.4). Median ΔKPS for this subgroups were -10 (IQR -30/-10) in OFO 2 and 0 (IQR 0-10) in OFO 3a; median PFS was 8.0 months (IQR 6.0-9.0) in OFO 2 and 7.0 months (IQR 6.0-12.0) in OFO 3a; median OS was 16.0 months (IQR 12.0-22.0) in OFO 2 and 14.5 months (IQR 12.5-22.0) in OFO 3a.

Patients in subgroup OFO 3b (n = 119) were similar regarding ASA scores to subgroups 1b, 2 and 3a. Though, the median preoperative KPS (90, IQR 90-100) and NIHSS scores (0, IQR 0-1) were more beneficial in this group than in the other subgroups. Like in subgroup 1b, a high proportion of resections was done with intraoperative mapping (26.1%), intraopera-

tive ultrasound (12.6%) or intraoperative fluorescence (24.4%) and the median extent of resection was 100% (IQR 96.8-100.0). However, their median postoperative ΔKPS was the worst of all subgroups (-20 (-30/-20). Notably, the PFS was almost identical to OFO 1b (median 12.0 months, IQR 10.5-16.5) and the OS was the best of all subgroups (median 28.5 months, IQR 23.5-41.5).

DISCUSSION

Key results

Currently, postoperative outcomes in glioblastoma patients such as extent of resection, neurological deficits, and survival are primarily analyzed and evaluated as separate entities. However, a strong interplay between these factors exists and forms the basis of the resection's rationale. The association of extent of resection and survival outcomes in glioblastoma patients has been an important topic of interest [5-12]. Moreover, previous studies have evaluated the prognostic value of neurological morbidity [13,14] and have identified poor KPS as a negative prognostic factor in these patients [10,15,16]. To our knowledge, this study is the first to present a practical grading scale to divide glioblastoma patients based on their individual postoperative [change in] KPS or NIHSS score combined with extent of resection. Our analyses were based on a patient cohort of 848 primary eloquent glioblastoma patients (selected from 2691 patients), which are to our knowledge the largest cohorts of glioblastoma patients that has been published. The presented onco-functional outcome (OFO) assists with identifying clinically different patient subgroups in order to compare and analyze surgical outcomes more effectively. The OFO grading scale divided our combined cohort of glioblastoma patients in 5 subgroups: OFO 1a, 1b, 2, 3a and 3b. OFO subgroups 1a, 2 and 3a are distinct from each other primarily due to differences in EOR. In contrast, OFO subgroups 1a, 1b and 3b are distinct from each other primarily due to differences in ΔNIHSS-EOR or ΔKPS.

Interpretation

We tested the ΔNIHSS-EOR and ΔKPS-EOR to evaluate which model would perform best in identifying subgroups with potentially different survival outcomes. The ΔNIHSS-EOR model at 6 weeks shows that the OFO 1b subgroup had the best median overall survival (18 months), which was significantly longer than OFO subgroups 1a and 2 (8.5 and 8.0 months) and also OFO 3a and 3b (4.0 and 2.0 months). PFS did not differ between groups ($p = 0.12$). Patients in OFO subgroup 1b did not differ from other subgroups in terms of age ($p = 0.77$) or *IDH* status ($p = 0.21$), MGMT status ($p = 0.37$). Though, their median preoperative KPS was slightly better (90 vs 80 for the other subgroups, $p < 0.001$), a substantial amount of the resections was performed with intraoperative mapping (20.2%, $p < 0.001$), ultrasound

(14.4%) or fluorescence (19.3% p = 0.0021), and many of the patients received adjuvant chemotherapy and radiotherapy (90.1%, p < 0.001). All of those factors might explain why their overall survival was significantly longer than the other subgroups. The postoperative NIHSS score of patients in OFO 1a improved a lot (median -3), but they also had a much higher preoperative median NIHSS score (3, IQR 2-5, p < 0.001) and a substantial proportion of those patients was operated with the use of intraoperative mapping (13.9%), ultrasound (16.7%) or fluorescence (27.8%). Patients in OFO 2 had a similar median overall survival to OFO 1b patients, even though their preoperative NIHSS score was significantly better (median 1, p < 0.001) and their KPS was similar (median 80, IQR 70-80). However, a smaller proportion of patients in OFO 2 was operated with the use of intraoperative mapping (4.2%), ultrasound (10.0%) or fluorescence (8.3%), a lower percentage of patients received adjuvant chemotherapy and radiotherapy (79.2%) and the median EOR in this subgroup was 74.4%.

OFO subgroups 3a and 3b experienced the worst median overall survival (4.0 months and 2.0 months respectively). This cannot be fully explained by preoperative KPS or NIHSS scores, which were comparable or even better than the other subgroups (median pre-op KPS: 80; median pre-op NIHSS score: 1 for OFO 3a and 0 for OFO 3b). However, a lower proportion of patients received adjuvant chemotherapy and radiotherapy (OFO 3a: 72.6%; OFO 3b: 50.0%). The median EOR was significantly lower in OFO 3a (43.2%) but significantly higher in OFO 3b (92.9%), which might be explained by the fact that in OFO 3b, the proportion of resections done with intraoperative mapping (14.3%), ultrasound (21.4%) or fluorescence (25.0%) was significantly higher. This hypothesis is underlined by the fact that OFO 1a and OFO 1b also had high percentages of resections with mapping or adjuncts and high median extents of resection.

The ΔNIHSS-EOR model at 6 months postoperatively has similar features as the 6 weeks model and divides the cohort largely by the same lines. Only patients that had received adjuvant chemotherapy and radiotherapy were included in the 6 months analysis to minimize confounding. This naturally translates to longer median OS values for all subgroups as compared with the 6 weeks analysis. The fact that the median OS of OFO 2 is comparable with OFO 1b and 1a (even though the median EOR in OFO 2 was substantially lower, 74.6%) can be explained by higher proportion of *IDH*-mutant patients in this subgroup. Moreover, the fact that OFO 3a and 3b experienced the worst median OS values – even though 100% received adjuvant chemotherapy and radiotherapy and the preoperative scores were relatively similar to the other subgroups – could be explained by the low median EOR (OFO 3a) and suboptimal neurological status at 6 months (OFO 3b).

The ΔKPS-EOR produced mixed results. The model at 6 weeks postoperatively shows preoperative KPS and NIHSS scores that are relatively comparable between subgroups. The OFO 1a, OFO 1b and OFO 3b subgroups that this model identifies are very similar to these subgroups according to the ΔNIHSS-EOR model. Though, characteristics of OFO 2 and OFO 3a differed in the ΔKPS-EOR from the ΔNIHSS-EOR model. The ΔKPS-EOR model showed that these patients had the best median OS of all subgroups (OFO 2: 19.0 months; OFO 3a: 17.0 months), even though the median EOR in these groups was fairly low (OFO 2: 64.4%; OFO 3a: 37,8%). However, these subgroups had the largest proportion of patients that received both adjuvant chemotherapy and radiotherapy, which proves to be a strong prognostic factor in our dataset. Furthermore, OFO 3 patients experienced a median improvement in KPS by 10 points postoperatively.

In summary, we conclude that patients in OFO subgroup 1a consisted of patients with a considerable amount of preoperative neurological morbidity but were selected for maximum safe resection, often with the use of intraoperative mapping or adjuncts, which resulted in a greatly improved postoperative KPS and NIHSS score and high EOR. OFO subgroup 1b also consisted of patients that were selected for maximum safe resection, but these patients were in a much better neurological condition preoperatively, which explains their similar KPS and NIHSS scores preoperatively and postoperatively, along with a high median EOR. In these patients, the surgeon has succeeded in selecting preoperatively "fit" patients to undergo maximum safe resection with preservation of neurological function, which leads to improved OS. Based on our data, a viable explanation for the significant difference in median OS between these groups (OFO 1a: 18.0 months; OFO 1b: 8.5 months) could be explained by differences in preoperative KPS and NIHSS scores. This means that aggressive surgery cannot fully nullify the negative prognostic effects of suboptimal preoperative factors such as diminished neurological functioning.

Furthermore, we hypothesize that OFO 2 was an "in-between group" that consisted of patients that were very similar to patients in OFO 1a as for preoperative status, but did not receive adjuvant chemotherapy and radiotherapy as much as OFO 1a and had a much lower median EOR. The surgeon was not able to operate aggressively which led to a lower median EOR and higher residual tumor volumes. Surgeons can opt to be more defensive for a variety of reasons: one example would be patients with tumors in which the eloquence of the tumor combined with the absence of intraoperative mapping or surgical adjuncts did not allow them to pursue maximum safe resection. Consequently, these patients did not experience an increase in NIHSS score postoperatively, but they received less often adjuvant chemotherapy and radiotherapy, which might have severely hampered their overall survival – which also applies to OFO 3a. Notably, the ΔKPS-EOR differed from the ΔNIHSS-EOR for this group, since in this model OFO 2 patients had the best median OS and received in >95%

of cases adjuvant chemotherapy and radiotherapy. Thus, ΔNIHSS might be a better predictor to make a distinction between OFO 1a, 1b and 2. The main difference between OFO 2 and OFO 3a is the median EOR, which might have negatively influenced the median OS for OFO 3a. OFO 3b patients consisted of the group with significant postoperative worsening in neurology and functioning – even though a substantial proportion of resections was done with intraoperative mapping or adjuncts. This group might be comprised of patients in which the surgeon pursued maximum safe resection but incurred neurological deficits (e.g. due to damage to cortical or subcortical tracts, postoperative ischemia, rebleeds), which limited these patients' ability to undergo adjuvant chemotherapy and radiotherapy due to their suboptimal KPS and NIHSS scores, which consequently impacted their OS negatively.

Limitations

This retrospective cohort includes patients from 3 large university referral hospitals which might skew the results towards a typical patient distribution of tertiary centers. We therefore invite colleagues to test the validity of our models in their own centers and patient cohorts to test the external generalizability. Moreover, since the patients in our cohort all received tumor resection rather than biopsy, our OFO models might not represent the full range of glioblastoma patients but rather subgroups of patients with resectable glioblastoma. Last, our study describes a proof-of-concept which needs to be validated with a second external dataset.

CONCLUSIONS

This study is the first, to our knowledge, to combine extent of resection and neurological morbidity or extent of resection with patient functioning in order to create a novel outcome for glioblastoma patients. The current study presents a proof-of-concept of this onco-functional outcome (OFO) and is based on a large cohort of 848 patients. This new tool enables neurosurgeons to assess two important postoperative parameters simultaneously and includes 5 clinically different patient subgroups with distinct survival outcomes. The ΔNIHSS-EOR model is better than the ΔKPS-EOR model at distinguishing between the OFO subgroups. Moreover, the ΔNIHSS-EOR model at 6 weeks proved to be best for comparing OFO subgroups based on postoperative morbidity and EOR, while the ΔNIHSS-EOR model at 6 months postoperatively yielded the best results for comparing survival outcomes. The OFO grading scale has great potential to assist with identifying clinically different patient subgroups in order to compare and analyze surgical outcomes more effectively.

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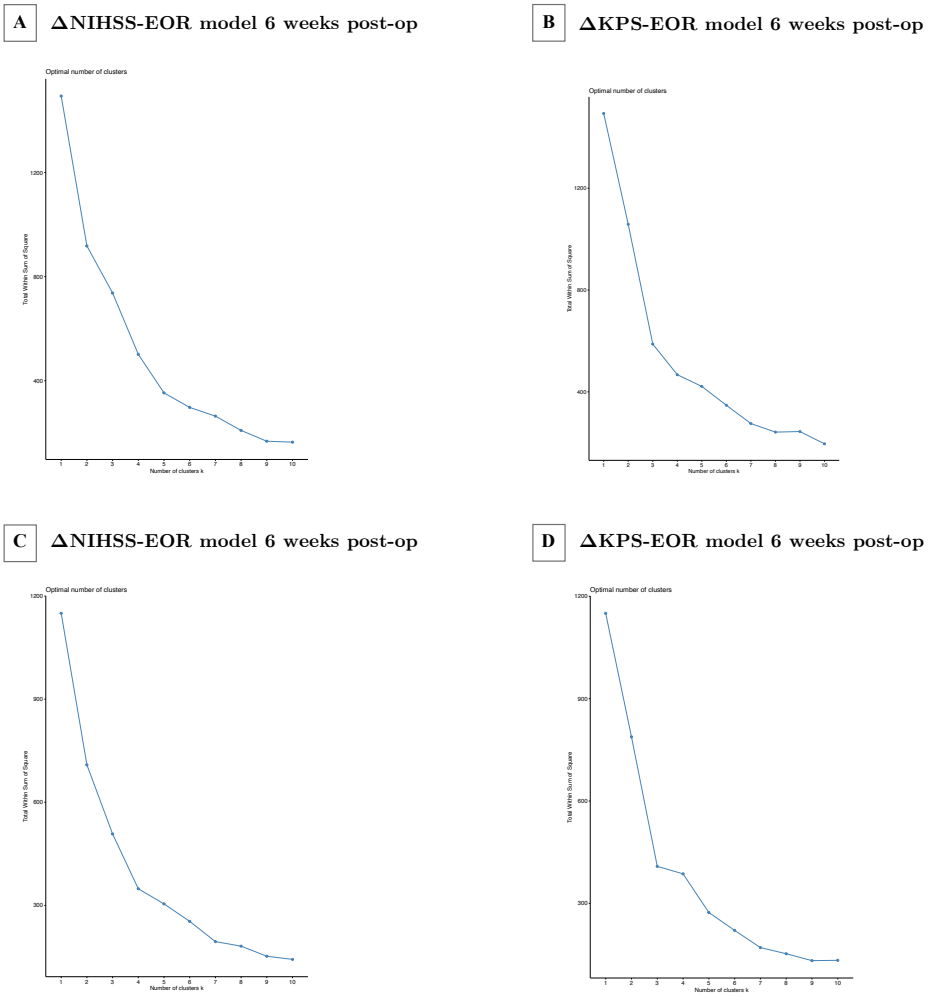
DATA SUPPLEMENT

eMethods 1: Details and Cohorts

Data collection

All patients with glioblastoma surgery between January 2010 and October 2020 at the Erasmus Medical Center, Haaglanden Medical Center and University Hospital Leuven were screened for eligibility (n = 2691). Inclusion criteria were (1) resection (excluding biopsy), (2) histopathological diagnosis of primary glioblastoma (excluding grade II/III gliomas with malignant transformation and recurrent glioblastomas), (3) eloquent or near-eloquent location of the tumor, (4) unifocal enhancing lesion (excluding multifocal enhancing lesions), (4) availability of clinical and radiological data in electronic patient file. After exclusion of 1843 patients, 848 patients with tumor resection for primary, eloquent glioblastoma were eligible for inclusion in the analysis subsets. Subsequently, 748 patients were included in the subset at 6 weeks postoperatively, and 575 patients in the subset at 6 months postoperatively (Figure 1). Patients that had not received adjuvant chemotherapy and radiotherapy were excluded from the 6 months subset to minimize the risk of confounding neurological morbidity, clinical functioning, and survival outcomes. Collected data included patient demographics, preoperative functioning (KPS, NIHSS), comorbidities (ASA), tumor related factors (location by lobe and hemisphere), molecular factors (IDH status, MGMT status), surgical factors (intraoperative electrophysiological mapping, intraoperative ultrasound, intraoperative fluorescence), adjuvant therapy, postoperative functioning (KPS and NIHSS at 6 weeks and 6 months), volumetric tumor data and survival data (Tables 1 and 2). Tumor volumes were assessed both preoperatively and postoperatively with volumetric measurements on T1-weighted post-gadolinium images based on the contrast-enhancing (CE) part of the tumor. Extent of resection was calculated as (pre-operative tumor volume – post-operative tumor volume)/pre-operative tumor volume x 100%. Preoperative scans were obtained within 24 hours prior to resection and postoperative scans were obtained within 72 hours after resection. Postoperative T1-weighted post-gadolinium MR-images were compared with DWI-sequences to exclude induced edema or ischemia in the tumor volumetrics.



eFigure 1: Elbow plots for OFO models – ΔNIHSS-EOR model at 6 weeks postoperatively

eTable 1: Demographic table for Erasmus MC, Haaglanden MC and UZ Leuven Cohorts

Characteristic	EMC-Cohort (n = 382)	HMC-Cohort (n = 354)	Leuven-Cohort (n = 111)	*p* value
Gender				0.25[b]
Male	236/382 (61.2)	221/354 (62.4)	78/111 (70.3)	
Female	146/382 (38.2)	133/354 (37.6)	33/111 (29.7)	
Age at diagnosis, years				<0.001[a]
Mean (SD)	61.2 (10.9)	64.8 (11.1)	60.5 (11.8)	
Median (IQR)	62.5 (54-70)	67.0 (58.0-73.0)	64.0 (52.0-69.0)	
Range	22.0-82.0	25.0-89.0	20.0-85.0	
Preoperative KPS				<0.001[b]
<60	4/382 (1.0)	8/354 (2.3)	1/111 (0.9)	
60	19/382 (5.0)	23/354 (6.5)	2/111 (1.8)	
70	76/382 (19.9)	49/354 (13.8)	7/111 (6.3)	
80	122/382 (31.9)	105/354 (30.0)	26/111 (23.4)	
90	108/382 (28.3)	138/354 (39.0)	53/111 (47.7)	
100	53/382 (13.9)	31/354 (8.8)	22/111 (19.8)	
Median preoperative KPS (IQR)	80 (70-90)	80 (80-90)	90 (80-90)	
Preoperative ASA score				<0.001[b]
I	67/381 (17.6)	33/354 (9.3)	6/111 (5.4)	
II	257/381 (67.5)	244/354 (68.9)	52/111 (46.8)	
III	56/381 (14.7)	75/354 (21.2)	51/111 (45.9)	
IV	1/381 (0.3)	2/354 (0.6)	2/111 (1.8)	
Median preoperative ASA score (IQR)	2 (2-2)	2 (2-2)	2 (2-3)	
Preoperative NIHSS score				<0.001[b]
0	138/382 (36.1)	115/354 (32.5)	21/111 (18.9)	
1	125/382 (32.7)	95/354 (26.8)	28/111 (25.2)	
2	82/382 (21.5)	61/354 (17.2)	21/111 (18.9)	
3	19/382 (5.0)	31/354 (8.8)	14/111 (12.6)	
4	8/382 (2.1)	23/354 (6.5)	10/111 (9.0)	
>4	10/382 (2.6)	29/354 (8.2)	17/111 (15.3)	
Median preoperative NIHSS score (IQR)	1 (0-2)	1 (0-2)	2 (1-3)	

eTable 1: Demographic table for Erasmus MC, Haaglanden MC and UZ Leuven Cohorts (continued)

Characteristic	EMC-Cohort (n = 382)	HMC-Cohort (n = 354)	Leuven-Cohort (n = 111)	*p* value
Tumor location by lobe				<0.001[b]
Frontal	120/382 (31.4)	118/354 (33.3)	33/111 (29.7)	
Parietal	84/382 (22.0)	95/354 (26.8)	34/111 (30.6)	
Temporal	152/382 (39.8)	126/354 (35.6)	26/111 (23.4)	
Occipital	26/382 (6.8)	15/354 (4.2)	18/111 (16.2)	
Tumor location by hemisphere				0.074[b]
Left	219/382 (57.3)	176/354 (49.7)	65/111 (58.6)	
Right	163/382 (42.7)	178/354 (50.3)	46/111 (41.4)	
IDH status				0.0023[b]
Wildtype	157/164 (95.7)	248/286 (86.7)	88/93 (94.6)	
Mutant	7/164 (4.2)	38/286 (13.3)	5/93 (5.4)	
MGMT status				<0.001[b]
Methylated	99/189 (52.4)	93/344 (27.0)	10/29 (34.5)	
Unmethylated	90/189 (47.6)	251/344 (73.0)	19/29 (65.5)	
Mapping and surgical adjuncts				<0.001[b]
Intraoperative electrophysiological mapping	41/382 (10.7)	24/354 (6.8)	27/111 (24.3)	
Intraoperative ultrasound	73/382 (19.1)	0/354 (0.0)	0/111 (0.0	
Intraoperative fluorescence	25/382 (6.5)	17/354 (4.8)	110/111 (99.1)	
Postoperative adjuvant therapy				<0.0013[b]
Radiotherapy only	45/382 (11.8)	37/354 (10.5)	7/111 (6.3)	
Chemotherapy only	7/382 (1.8)	3/354 (0.8)	4/111 (3.6)	
Both	282/382 (73.8)	260/354 (73.4)	100/111 (90.1)	
None	48/382 (12.6)	54/354 (15.3)	0/111 (0.0)	
Preoperative CE tumor volume, ml				<0.001[a]
Mean (SD)	59.5 (52.5)	78.5 (57.3)	32.6 (22.6)	
Median (Q1-Q3)	45.1 (24.3-80.8)	63.3 (35.8-119.3)	29.2 (14.3-49.8)	
Range	0.4-237.0	0.7-237.6	0.75-113.2	

eTable 1: Demographic table for Erasmus MC, Haaglanden MC and UZ Leuven Cohorts (continued)

Characteristic	EMC-Cohort (n = 382)	HMC-Cohort (n = 354)	Leuven-Cohort (n = 111)	*p* value
Postoperative CE tumor volume, ml				<0.001[a]
Mean (SD)	7.4 (14.7)	6.0 (12.2)	0.95 (3.3)	
Median (Q1-Q3)	2.1 (0.3-6.8)	1.8 (0-5.7.0)	2.9 (1.4-5.0)	
Range	0.0-94.0	0.0-93.7	0.0-26.4	
Extent of resection CE tumor, % by volume				<0.001[a]
Mean (SD)	90.0 (12.8)	91.6 (13.6)	94.0 (9.7)	
Median (Q1-Q3)	94.3 (85.9-98.6)	97.1 (88.4-100.0)	97.6 (94.0-99.0)	
Range	8.9-100.0	9.0-100.0	54.5-100.0	
Median progression-free survival, months (IQR)	6.0 (3.0-10.0)	12.0 (4.0-25.5)	10.5 (6.0-15.75)	<0.001[a]
Median overall survival, months (IQR)	11.0 (6.0-17.9)	15.5 (5.5-28.0)	16.0 (11.0-23.5)	<0.001[a]

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 between the Erasmus MC, Haaglanden MC and UZ Leuven cohorts using linear model ANOVA[a] and Pearson's chi-square test[b].

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing.

eTable 2: Summary data of the OFO subgroups – ΔNIHSS-EOR model at 6 weeks postoperatively

Characteristic	OFO 1a (n = 72)	OFO 1b (n = 466)	OFO 2 (n = 120)	OFO 3a (n = 62)	OFO 3b (n = 28)	*p* value
Gender						0.027[b]
Male	36/72 (50.0)	304/466 (65.2)	71/120 (59.2)	31/62 (50.0)	19/28 (68.9)	
Female	36/72 (50.0)	162/466 (34.8)	49/120 (40.1)	31/62 (50.0)	9/28 (32.1)	
Age at diagnosis, years						0.77[a]
Mean (SD)	62.3 (11.2)	61.4 (11.6)	62.0 (10.0)	62.7 (9.6)	59.6 (10.6)	
Median (IQR)	65.0 (56.0-69.0)	62.0 (54.0-70.0)	63.0 (53.5-70.0)	63.5 (58.0-69.0)	59.0 (52.5-68.0)	
Range	32.0-75.0	20.0-89.0	22.0-81.0	36.0-80.0	24.0-75.0	
Preoperative KPS						<0.001[b]
<60	6/72 (8.3)	1/466 (0.2)	0/120 (0.0)	1/62 (1.6)	1/28 (3.6)	
60	8/72 (11.1)	14/466 (3.0)	7/120 (5.8)	2/62 (3.2)	1/28 (3.6)	
70	12/72 (16.7)	52/466 (11.1)	25/120 (20.8)	10/62 (1.6)	5/28 (17.9)	
80	28/72 (38.9)	129/466 (27.7)	29/120 (24.2)	24/62 (38.7)	11/28 (39.3)	
90	16/72 (22.2)	191/466 (40.1)	49/120 (40.8)	19/62 (30.6)	6/28 (21.4)	
100	2/72 (2.8)	79/466 (17.0)	10/120 (8.3)	6/62 (9.7)	4/28 (14.3)	
Median preoperative KPS (IQR)	80 (70-80)	90 (80-90)	80 (70-90)	80 (80-90)	80 (70-85)	
Preoperative ASA score						0.032[b]
I	7/71 (9.9)	59/454 (13.0)	16/120 (13.3)	13/61 (21.3)	3/28 (10.7)	
II	40/71 (56.3)	277/454 (61.0)	84/120 (70.0)	42/61 (68.9)	21/28 (75.0)	
III	21/71 (29.6)	114/454 (25.1)	20/120 (16.7)	6/61 (9.8)	4/28 (14.3)	
IV	3/71 (4.2)	4/454 (0.9)	0/120 (0.0)	0/61 (0.0)	0/28 (0.0)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-3)	2 (2-2)	2 (2-2)	2 (2-2)	
Preoperative NIHSS score						<0.001[b]
0	0/72 (0.0)	184/466 (39.5)	46/120 (38.3)	24/62 (38.7)	15/28 (53.6)	
1	0/72 (0.0)	158/466 (33.9)	37/120 (30.8)	18/62 (29.0)	6/28 (21.4)	
2	24/72 (33.3)	75/466 (16.1)	26/120 (21.7)	12/62 (19.4)	4/28 (14.3)	
3	14/72 (19.4)	29/466 (6.2)	5/120 (4.2)	5/62 (8.1)	1/28 (3.6)	
4	10/72 (13.9)	11/466 (2.4)	4/120 (3.3)	1/62 (1.6)	1/28 (3.6)	
>4	24/72 (33.3)	9/466 (1.9)	2/120 (1.7)	2/62 (3.2)	1/28 (3.6)	
Median preoperative NIHSS score (IQR)	3 (2-5)	1 (0-1)	1 (0-2)	1 (0-2)	0 (0-1)	

eTable 2: Summary data of the OFO subgroups – ΔNIHSS-EOR model at 6 weeks postoperatively (continued)

Characteristic	OFO 1a (n = 72)	OFO 1b (n = 466)	OFO 2 (n = 120)	OFO 3a (n = 62)	OFO 3b (n = 28)	*p* value
Tumor location by lobe						0.046[b]
Frontal	35/72 (48.6)	150/465 (32.3)	31/120 (25.8)	18/62 (29.0)	14/28 (50.0)	
Parietal	20/72 (27.8)	113/465 (24.3)	31/120 (25.8)	17/62 (27.4)	7/28 (25.0)	
Temporal	15/72 (20.8)	165 (35.5)	51/120 (42.5)	23/62 (37.1)	6/28 (21.4)	
Occipital	2/72 (2.8)	37 (8.0)	7/120 (5.8)	4/62 (6.5)	1/28 (3.6)	
Tumor location by hemisphere						0.21[b]
Left	35/72 (48.6)	266/466 (57.1)	75/120 (62.5)	31/62 (50.0)	13/28 (46.4)	
Right	37/72 (51.4)	200/466 (42.9)	45/120 (37.5)	31/62 (50.0)	15/28 (53.6)	
IDH status						
Wildtype	49/50 (98.0)	310/328 (94.5)	46/51 (90.2)	15/15 (100.0)	15/15 (100.0)	0.57[b]
Mutant	1/50 (2.0)	18/328 (5.5)	5/51 (9.8)	0/15 (0.0)	0/15 (100.0)	
MGMT status						0.37[b]
Methylated	15/48 (31.3)	133/327 (40.7)	27/69 (39.1)	10/18 (55.6)	7/15 (46.7)	
Unmethylated	33/48 (68.8)	194/327 (59.3)	42/69 (60.9)	8/18 (44.4)	8/15 (53.3)	
Mapping and surgical adjuncts						
Intraoperative electrophysiological mapping	10/72 (13.9)	94/466 (20.2)	5/120 (4.2)	0/62 (0.0)	4/28 (14.3)	<0.001[b]
Intraoperative ultrasound	12/72 (16.7)	67/466 (14.4)	12/120 (10.0)	3/62 (4.8)	6/28 (21.4)	0.10[b]
Intraoperative fluorescence	20/72 (27.8)	90/466 (19.3)	10/120 (8.3)	6/62 (9.7)	7/28 (25.0)	0.0021[b]
Postoperative adjuvant therapy						<0.001[b]
Radiotherapy only	2/72 (2.8)	23 (4.9)	3 (2.5)	13/62 (21.0)	2/28 (7.1)	
Chemotherapy only	0/72 (0.0)	7 (1.5)	11 (9.2)	0/62 (0.0)	1/28 (3.6)	
Both	69/72 (95.8)	422/465 (90.1)	95/120 (79.2)	45/62 (72.6)	14/28 (50.0)	
None	1/72 (1.4)	13 (2.8)	11 (9.2)	4/62 (6.5)	11/28 (39.3)	
Preoperative CE volume, ml						0.0017[a]
Mean (SD)	83.7 (56.5)	62.8 (54.5)	67.8 (45.2)	55.5 (45.1)	87.3 (89.1)	
Median (Q1-Q3)	75.4 (31.6-12.7)	49.8 (24.8-85.7)	45.0 (34.0-80.0)	40.6 (22.2-89.6)	55.2 (24.5-93.1)	
Range	0.5-167.0	1.3-208.0	1.6-219.0	0.4-171.0	10.0-203.0	

eTable 2: Summary data of the OFO subgroups – ΔNIHSS-EOR model at 6 weeks postoperatively (continued)

Characteristic	OFO 1a (n = 72)	OFO 1b (n = 466)	OFO 2 (n = 120)	OFO 3a (n = 62)	OFO 3b (n = 28)	*p* value
Postoperative CE volume, ml						<0.001[a]
Mean (SD)	5.1 (1.0)	2.5 (3.9)	15.8 (13.9)	32.7 (26.7)	14.2 (35.8)	
Median (Q1-Q3)	1.26 (0-4.8)	1.11 (0-3.6)	12.7 (5.2-21.5)	25.2 (12.7-48.2)	1.4 (1.0-5.9)	
Range	0.0-47.0	0.0-29.0	0.0-61.2	0.2-94.6	0.0-69.0	
Extent of resection CE tumor, % by volume						<0.001[a]
Mean (SD)	94.8 (6.9)	96.1 (4.4)	72.6 (8.4)	39.1 (14.0)	89.1 (13.3)	
Median (Q1-Q3)	97.5 (93.3-99.9)	97.8 (93.3-100.0)	74.4 (65.3-79.8)	43.2 (31.9-49.7)	92.9 (84.2-98.8)	
Range	69.5-100.0	84.6-100.0	56.2-84.8	8.9-55.2	44.5-100.0	
Postoperative NIHSS score at 6 weeks						<0.001[b]
0	42/72 (58.3)	203/466 (43.6)	45/120 (37.5)	23/62 (37.1)	0/28 (0.0)	
1	16/72 (22.2)	106/466 (22.7)	25/120 (20.8)	18/62 (29.0)	0/28 (0.0)	
2	8/72 (11.1)	84/466 (18.0)	25/120 (20.8)	10/62 (16.1)	0/28 (0.0)	
3	3/72 (4.2)	40/466 (8.6)	10/125 (8.0)	5/62 (8.1)	0/28 (0.0)	
4	3/72 (4.2)	14/466 (3.0)	8/125 (6.4)	3/62 (4.8)	0/28 (0.0)	
>4	0/72 (0.0)	19/466 (4.1)	7/125 (5.6)	3/62 (4.8)	28/28 (100.0)	
Median postoperative NIHSS score at 6 weeks (IQR)	0 (0-1)	1 (0-2)	1 (0-2)	1 (0-2)	9.5 (6-12)	
ΔNIHSS[*]						<0.001[a]
Mean (SD)	-3.33 (1.98)	0.15 (1.00)	0.36 (1.23)	0.31 (1.39)	8.4 (3.3)	
Median (Q1-Q3)	-3 (-2/-4)	0 (0-0)	0 (0-1)	0 (0-1)	7.5 (5-12)	
Range	-2/-11	-1/4	-2/2	-2/5	5-15	
Median progression-free survival, months[±]	7.8 (5.0-11.0)	8.0 (7.0-9.0)	8.0 (7.0-8.0)	4.0 (3.0-4.0)	2.0 (2.0-2.0)	0.12[c]
Median overall survival, months[±]	8.5 (8.0-38.5)	18.0 (17.0-19.0)	10.0 (7.5-11.5)	10.8 (8.0-14.0)	8.8 (6.0-14.0)	<0.001[c]

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 between the various OFO subgroups of the ΔNIHSS-EOR model at 6 weeks postoperatively using linear model ANOVA[a], Pearson's chi-square test[b] and log-rank test[c].

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing.

[*]With preoperative score as reference

[±]95% Confidence Interval.

eTable 3: Summary data of the OFO subgroups – ΔKPS-EOR model at 6 weeks postoperatively

Characteristic	OFO 1a (n = 162)	OFO 1b (n = 378)	OFO 2 (n = 98)	OFO 3a (n = 40)	OFO 3b (n = 70)	*p* value
Gender						0.036[b]
Male	87/162 (53.7)	237/378 (63.3)	59/98 (60.2)	31/40 (77.5)	48/70 (68.6)	
Female	75/162 (46.3)	141/378 (37.3)	39/98 (39.8)	9/40 (22.5)	22/70 (31.4)	
Age at diagnosis, years						0.18[a]
Mean (SD)	62.9 (9.2)	61.1 (11.4)	62.3 (12.0)	59.5 (11.2)	61.0 (12.3)	
Median (IQR)	64.0 (57.3-70.0)	62.0 (54.0-70.0)	63.0 (55.0-71.0)	62.0 (53.3-67.5)	64.0 (52.0-70.0)	
Range	36.0-81.0	22.0-89.0	23.0-87.0	33.0-78.0	20.0-85.0	
Preoperative KPS						0.0051[b]
<60	1/162 (0.6)	4/378 (1.1)	2/98 (2.0)	1/40 (2.5)	1/70 (1.4)	
60	8/162 (4.9)	20/378 (5.3)	3/98 (3.1)	1/40 (2.5)	0/70 (0.0)	
70	32/162 (19.8)	55/378 (14.6)	11/98 (11.2)	1/40 (2.5)	5/70 (7.1)	
80	52/162 (32.1)	114/378 (30.2)	28/98 (28.6)	9/40 (22.5)	18/70 (25.7)	
90	59/162 (36.4)	129/378 (34.1)	41/98 (41.8)	23/40 (57.5)	29/70 (41.4)	
100	10/162 (6.2)	56/378 (14.8)	13/98 (13.3)	5/40 (12.5)	17/70 (24.3)	
Median preoperative KPS (IQR)	80 (70-90)	80 (80-90)	90 (80-90)	90 (80-90)	90 (80-90)	
Preoperative ASA score						<0.0001[b]
I	28/161 (17.4)	50/369 (13.6)	13/95 (13.7)	3/39 (7.7)	4/70 (5.7)	
II	112/161 (69.6)	237/369 (64.2)	62/95 (65.3)	18/39 (46.2)	35/70 (50.0)	
III	21/161 (13.0)	78/369 (21.1)	19/95 (20.0)	17/39 (43.6)	30/70 (42.9)	
IV	0/161 (0.0)	4/369 (1.1)	1/95 (1.1)	1/39 (2.6)	1/70 (1.4)	
Median preoperative ASA score (IQR)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-3)	2 (2-3)	
Preoperative NIHSS score						0.025[b]
0	61/162 (37.7)	144/378 (38.1)	40/98 (40.8)	12/40 (30.0)	12/70 (17.1)	
1	46/162 (28.4)	114/378 (30.2)	32/98 (32.7)	9/40 (22.5)	18/70 (25.7)	
2	34/162 (21.0)	70/378 (18.5)	15/98 (15.3)	8/40 (20.0)	14/70 (20.0)	
3	11/162 (6.8)	24/378 (6.3)	5/98 (5.1)	3/40 (7.5)	11/70 (15.7)	
4	6/162 (3.7)	10/378 (2.6)	2/98 (2.0)	4/40 (10.0)	5/70 (7.1)	
>4	4/162 (2.5)	16/378 (4.2)	4/98 (4.1)	4/40 (10.0)	10/70 (14.3)	
Median preoperative NIHSS score (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-3)	2 (1-3)	

eTable 3: Summary data of the OFO subgroups – ΔKPS-EOR model at 6 weeks postoperatively (continued)

Characteristic	OFO 1a (n = 162)	OFO 1b (n = 378)	OFO 2 (n = 98)	OFO 3a (n = 40)	OFO 3b (n = 70)	*p* value
Tumor location by lobe						0.026[b]
Frontal	45/162 (27.8)	133/377 (35.3)	38/98 (38.8)	8/40 (20.0)	24/70 (34.3)	
Parietal	41/162 (25.3)	93/377 (24.7)	20/98 (20.4)	13/40 (32.5)	20/70 (28.6)	
Temporal	66/162 (40.7)	132/377 (35.0)	33/98 (33.7)	12/40 (30.0)	17/20 (85.0)	
Occipital	10/162 (6.2)	19/377 (5.0)	7/98 (7.1)	7/40 (17.5)	9/20 (45.0)	
Tumor location by hemisphere						0.33[b]
Left	90/162 (55.6)	208/378 (55.0)	54/98 (55.1)	29/40 (72.5)	39/70 (55.7)	
Right	72/162 (44.4)	170/378 (45.0)	44/98 (44.9)	11/40 (27.5)	31/70 (44.3)	
IDH status						<0.001[b]
Wildtype	52/53 (98.1)	227/240 (94.6)	67/71 (94.4)	35/36 (97.2)	55/59 (93.2)	
Mutant	1/53 (1.9)	13/240 (5.4)	4/71 (5.6)	1/36 (2.8)	4/59 (6.8)	
MGMT status						0.65[b]
Methylated	35/74 (47.3)	109/282 (38.7)	37/89 (41.6)	5/16 (31.3)	6/16 (37.5)	
Unmethylated	39/74 (52.7)	173/282 (61.3)	52/89 (58.4)	11/16 (68.7)	10/16 (62.5)	
Mapping and surgical adjuncts						
Intraoperative electrophysiological mapping	7/162 (4.3)	65/378 (17.2)	17/98 (17.3)	11/40 (27.5)	18/70 (25.7)	<0.001[b]
Intraoperative ultrasound	15/162 (9.3)	70/378 (18.5)	14/98 (14.3)	2/40 (5.0)	0/70 (0.0)	<0.001[b]
Intraoperative fluorescence	10/162 (6.2)	19/378 (5.0)	6/98 (6.1)	24/40 (60.0)	70/70 (100.0)	<0.001[b]
Postoperative adjuvant therapy						<0.001[b]
Radiotherapy only	22/162 (13.6)	21/377 (5.6)	1/97 (1.0)	1/40 (2.5)	7/40 (17.5)	
Chemotherapy only	3/162 (1.9)	4/377 (1.1)	0/97 (0.0)	0/40 (0.0)	3/40 (7.5)	
Both	120/162 (74.1)	331/377 (87.8)	94/97 (96.9)	39/40 (97.5)	30/40 (75.0)	
None	17/162 (10.5)	21/377 (5.6)	2 (2.1)	0/40 (0.0)	0/40 (0.0)	
Preoperative CE volume, ml						<0.001[a]
Mean (SD)	71.1 (55.3)	62.3 (52.9)	63.2 (54.0)	53.2 (47.3)	56.5 (60.2)	
Median (Q1-Q3)	60.2 (27.2-97.8)	49.1 (24.8-87.9)	49.4 (23.2-83.8)	39.0 (22.5-68.6)	39.2 (19.9-67.2)	
Range	2.7-212.0	1.3-212.0	1.6-219.0	0.4-220.0	2.9-204.0	

eTable 3: Summary data of the OFO subgroups – ΔKPS-EOR model at 6 weeks postoperatively (continued)

Characteristic	OFO 1a (n = 162)	OFO 1b (n = 378)	OFO 2 (n = 98)	OFO 3a (n = 40)	OFO 3b (n = 70)	*p* value
Postoperative CE volume, ml						0.34[a]
Mean (SD)	5.2 (7.9)	2.9 (4.7)	23.7 (23.3)	33.1 (29.4)	2.7 (4.6)	
Median (Q1-Q3)	2.0 (0.9-6.1)	1.2 (0.0-4.3)	16.7 (9.2-31.0)	24.9 (13.4-40.5)	1.1 (0.0-2.8)	
Range	0.0-37.8	0.0-41.0	0.7-45.6	0.2-94.6	0.0-23.5	
Extent of resection CE tumor, % by volume						<0.001[a]
Mean (SD)	93.0 (8.3)	95.2 (5.7)	62.9 (11.2)	35.4 (15.6)	94.9 (6.0)	
Median (Q1-Q3)	95.7 (88.9-99.5)	97.6 (92.1-100.0)	64.4 (54.8-71.9)	37.8 (25.4-49.0)	97.3 (92.3-100.0)	
Range	64.3-100.0	78.31-100.0	27.9-80.0	8.9-58.2	77.6-100.0	
Postoperative KPS at 6 weeks						<0.001[b]
<60	0/162 (0.0)	6/378 (1.6)	7/98 (7.1)	0/40 (0.0)	20/70 (28.6)	
60	0/162 (0.0)	24/378 (6.3)	12/98 (12.2)	1/40 (2.5)	13/70 (18.6)	
70	10/162 (6.2)	51/378 (13.5)	26/98 (26.5)	4/40 (10.0)	24/70 (34.3)	
80	24/162 (14.8)	116/378 (30.7)	25/98 (25.6)	14/40 (35.0)	13/70 (18.6)	
90	78/162 (48.1)	153/378 (40.5)	26/98 (26.5)	17/40 (42.5)	0/70 (0.0)	
100	50/162 (30.9)	28/378 (7.4)	2/98 (2.0)	4/40 (10.0)	0/70 (0.0)	
Median postoperative KPS at 6 weeks (IQR)	90 (90-100)	80 (80-90)	80 (70-90)	90 (80-90)	70 (50-70)	
ΔKPS						<0.001[a]
Mean (SD)	13.3 (8.3)	-3.7 (4.8)	-8.6 (10.6)	4.8 (10.1)	-26.3 (10.8)	
Median (IQR)	10 (10-10)	0 (-10/0)	-10 (-10/0)	10 (0-10)	-20 (-20/-30)	
Range	10-60	-10/0	-40/0	-10/30	-20/-80	
Median progression-free survival, months[±]	6.0 (5.0-7.0)	9.0 (8.0-9.5)	11.0 (8.0-14.0)	11.5 (10.0-17.0)	10.0 (9.0-11.0)	0.0011[c]
Median overall survival, months[±]	11.0 (10.0-12.5)	14.0 (13.0-16.0)	19.0 (16.0-31.5)	17.0 (14.0-23.5)	16.0 (12.5-19.5)	<0.001[c]

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 between the various OFO subgroups of the ΔKPS-EOR model at 6 weeks postoperatively using linear model ANOVA[a] and Pearson's chi-square test[b].

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing.

[*]With preoperative score as reference

[±]95% Confidence Interval.

eTable 4: Summary data of the OFO subgroups – ΔNIHSS-EOR model at 6 months postoperatively

Characteristic	OFO 1a (n = 32)	OFO 1b (n = 325)	OFO 2 (n = 76)	OFO 3a (n = 39)	OFO 3b (n = 104)	*p* value
Gender						0.21[b]
Male	23/32 (71.9)	210/325 (64.6)	44/76 (57.9)	30/39 (76.9)	62/104 (59.6)	
Female	9/32 (28.1)	115/325 (35.4)	32/76 (42.1)	9/39 (23.1)	42/104 (40.4)	
Age at diagnosis, years						0.11[a]
Mean (SD)	61.3 (10.3)	59.7 (12.0)	59.2 (10.0)	60.6 (9.2)	62.9 (9.7)	
Median (IQR)	65.0 (56.0-68.0)	61.0 (54.0-68.0)	59.0 (52.0-66.0)	62.0 (57.0-66.0)	63.5 (55.3-70.8)	
Range	37.0-76.0	20.0-89.0	22.0-81.0	36.0-79.0	39.0-79.0	
Preoperative KPS						<0.001[b]
<60	5/32 (15.6)	0/325 (0.0)	0/76 (0.0)	0/39 (0.0)	0/104 (0.0)	
60	4/32 (12.5)	6/325 (1.8)	0/76 (0.0)	1/39 (2.6)	6/104 (5.8)	
70	6/32 (18.8)	24/325 (7.4)	15/76 (19.7)	5/39 (12.8)	13/104 (12.5)	
80	12/32 (37.5)	98/325 (30.2)	16/76 (21.1)	15/39 (38.5)	35/104 (33.7)	
90	4/32 (12.5)	142/325 (43.7)	38/76 (50.0)	12/39 (30.8)	37/104 (35.6)	
100	1/32 (3.1)	55/325 (16.9)	7/76 (9.2)	6/39 (15.4)	22/104 (21.2)	
Median preoperative KPS (IQR)	80 (60-80)	90 (80-90)	90 (80-90)	80 (80-90)	90 (80-90)	
Preoperative ASA score						0.032[b]
I	2/32 (6.3)	48/312 (15.4)	13/76 (17.1)	12/39 (30.8)	12/104 (11.5)	
II	19/32 (59.4)	187/312 (60.0)	52/76 (68.4)	25/39 (64.1)	68/104 (65.4)	
III	9/32 (28.1)	73/312 (23.4)	11/76 (14.5)	2/39 (5.1)	23/104 (22.1)	
IV	2/32 (6.3)	4/312 (1.3)	0/76 (0.0)	0/39 (0.0)	0/104 (0.0)	
Median preoperative ASA score (IQR)	3 (3-3)	2 (2-2)	2 (2-2)	2 (1-2)	2 (2-2)	
Preoperative NIHSS score						<0.001[b]
0	0/32 (0.0)	127/325 (39.1)	32/76 (42.1)	22/39 (56.4)	43/104 (41.3)	
1	0/32 (0.0)	111/325 (34.2)	18/76 (23.7)	7/39 (17.9)	28/104 (26.9)	
2	0/32 (0.0)	55/325 (16.9)	16/76 (21.1)	8/39 (20.5)	18/104 (17.3)	
3	8/32 (25.0)	23/325 (7.1)	4/76 (5.3)	1/39 (2.6)	6/104 (5.8)	
4	4/32 (12.5)	7/325 (2.2)	3/76 (3.9)	1/39 (2.6)	3/104 (2.9)	
>4	16/32 (50.0)	2/325 (0.6)	3/76 (3.9)	0/39 (0.0)	4/104 (3.8)	
Median preoperative NIHSS score (IQR)	5 (4-6)	1 (0-2)	1 (0-2)	0 (0-2)	1 (0-2)	

eTable 4: Summary data of the OFO subgroups – ΔNIHSS-EOR model at 6 months postoperatively (continued)

Characteristic	OFO 1a (n = 32)	OFO 1b (n = 325)	OFO 2 (n = 76)	OFO 3a (n = 39)	OFO 3b (n = 104)	*p* value
Tumor location by lobe						0.10[b]
Frontal	9/32 (28.1)	108/325 (33.2)	28/75 (37.3)	13/39 (33.3)	22/103 (21.4)	
Parietal	10/32 (31.3)	83/325 (25.5)	13/75 (17.3)	15/39 (38.5)	27/103 (26.2)	
Temporal	11/32 (34.4)	107/325 (32.9)	32/75 (42.7)	9/39 (23.1)	46/103 (44.7)	
Occipital	2/32 (6.3)	27/325 (8.3)	2/75 (2.7)	2/39 (5.1)	8/103 (7.8)	
Tumor location by hemisphere						0.72[b]
Left	22/32 (68.8)	186/325 (57.2)	46/76 (60.5)	21/39 (53.8)	61/104 (58.7)	
Right	10/32 (31.3)	139/325 (42.8)	30/76 (39.5)	18/39 (46.2)	43/104 (41.3)	
IDH status						<0.001[b]
Wildtype	25/26 (96.2)	234/250 (93.6)	34/38 (89.5)	9/9 (100.0)	58/104 (55.8)	
Mutant	1/26 (3.8)	16/250 (6.4)	4/38 (10.5)	0/9 (100.0)	46/104 (44.2)	
MGMT status						0.62[b]
Methylated	9/20 (45.0)	97/227 (42.7)	16/41 (39.0)	5/10 (50.0)	22/67 (32.8)	
Unmethylated	11/20 (55.0)	130/227 (57.3)	25/41 (61.0)	5/10 (50.0)	45/67 (67.2)	
Mapping and surgical adjuncts						
Intraoperative electrophysiological mapping	3/32 (9.4)	83/325 (25.6)	6/76 (7.9)	0/39 (0.0)	14/104 (13.5)	<0.001[b]
Intraoperative ultrasound	4/32 (12.5)	46/325 (14.2)	8/76 (10.5)	1/39 (2.6)	12/104 (11.5)	0.32[b]
Intraoperative fluorescence	12/32 (37.5)	101/325 (31.1)	5/76 (6.6)	5/39 (12.8)	23/104 (22.1)	<0.001[b]
Postoperative adjuvant therapy						NA
Radiotherapy only	0/32 (0.0)	0/325 (0.0)	0/76 (0.0)	0/39 (0.0)	0/104 (0.0)	
Chemotherapy only	0/32 (0.0)	0/325 (0.0)	0/76 (0.0)	0/39 (0.0)	0/104 (0.0)	
Both	32/32 (100.0)	325/325 (100.0)	76/76 (100.0)	39/39 (100.0)	104/104 (100.0)	
None	0/32 (0.0)	0/325 (0.0)	0/76 (0.0)	0/39 (0.0)	0/104 (0.0)	
Preoperative CE volume, ml						0.011[a]
Mean (SD)	71.7 (61.7)	53.8 (47.2)	59.0 (53.4)	47.4 (24.4)	58.0 (43.3)	
Median (Q1-Q3)	52.4 (24.3-102.5)	40.5 (21.7-70.8)	43.9 (22.3-78.1)	40.6 (33.0-18.5)	44.7 (24.0-84.5)	
Range	4.2-96.0	0.75-212.0	1.58-219.0	0.4-171.6	0.27-192.0	

eTable 4: Summary data of the OFO subgroups – ΔNIHSS-EOR model at 6 months postoperatively (continued)

Characteristic	OFO 1a (n = 32)	OFO 1b (n = 325)	OFO 2 (n = 76)	OFO 3a (n = 39)	OFO 3b (n = 104)	*p* value
Postoperative CE volume, ml						<0.001[a]
Mean (SD)	4.0 (9.4)	1.8 (3.4)	16.2 (16.5)	28.2 (24.4)	3.5 (6.8)	
Median (Q1-Q3)	0.3 (0.0-1.7)	0.38 (0-2.2)	11.3 (4.9-21.8)	19.8 (9.7-40.4)	1.0 (0.0-4.2)	
Range	0.0-36.1	0.0-29.9	0.55-93.7	0.2-94.6	0.0-40.0	
Extent of resection CE tumor, % by volume						<0.001[a]
Mean (SD)	96.0 (6.2)	96.8 (4.1)	73.6 (8.1)	39.8 (14.5)	94.5 (8.6)	
Median (Q1-Q3)	99.0 (95.5-100.0)	98.7 (94.4-100.0)	74.6 (67.3-80.7)	45.8 (29.6-50.9)	98.0 (92.7-100.0)	
Range	77.84-100.0	84.58-100.0	56.21-86.29	8.9-56.7	49.67-100.0	
Postoperative NIHSS score at 6 months						<0.001[b]
0	16/32 (50.0)	173/325	26/76 (34.2)	5/39 (12.8)	0/104 (0.0)	
1	10/32 (31.3)	74/325	16/76 (21.1)	13/39 (33.3)	0/104 (0.0)	
2	2/32 (6.3)	58/325	12/76 (15.8)	10/39 (25.6)	12/104 (11.5)	
3	2/32 (6.3)	15/325	11/76 (14.5)	7/39 (17.9)	28/104 (26.9)	
4	1/32 (3.1)	3/325	6/76 (7.9)	2/39 (5.1)	19/104 (18.3)	
>4	1/32 (3.1)	2/325	5/76 (6.6)	2/39 (5.1)	45/104 (43.3)	
Median postoperative NIHSS score at 6 months (IQR)	0.5 (0-1)	0 (0-1)	1 (0-3)	2 (1-3)	4 (3-5)	
ΔNIHSS[*]						<0.001[a]
Mean (SD)	-4.5 (1.7)	-0.21 (0.83)	0.45 (1.33)	0.48 (1.92)	3.5 (1.8)	
Median (Q1-Q3)	-4 (-3/-5)	0 (0/-1)	0 (0-1)	1 (0-2)	3 (2-4)	
Range	-3/-9	1/-2	4/-3	-1/9	-1/11	
Median progression-free survival, months[±]	15.0 (10.0-29.0)	12.0 (11.5-14.0)	9.0 (8.5-12.0)	7.0 (5.0-12.5)	7.0 (6.0-9.0)	<0.001[c]
Median overall survival, months[±]	28.0 (19.5-69.5)	27.0 (23.0-31.0)	22.0 (18.0-25.0)	12.5 (11.5-18.0)	14.0 (12.0-17.0)	<0.001[c]

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 between the various OFO subgroups of the ΔKPS-EOR model at 6 weeks postoperatively using linear model ANOVA[a] and Pearson's chi-square test[b].

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing.

[*]With preoperative score as reference.

eTable 5: Summary data of the OFO subgroups – ΔKPS-EOR model at 6 months postoperatively

Characteristic	OFO 1a (n = 147)	OFO 1b (n = 221)	OFO 2 (n = 62)	OFO 3a (n = 27)	OFO 3b (n = 119)	*p* value
Gender						0.70[b]
Male	94/147 (63.9)	143/221 (64.7)	36/62 (58.1)	20/27 (74.1)	76/119 (63.9)	
Female	53/147 (36.1)	78/221 (35.3)	26/62 (41.9)	7/27 (25.9)	43/119 (36.1)	
Age at diagnosis, years						0.29[a]
Mean (SD)	60.8 (9.7)	60.3 (12.3)	62.4 (9.1)	59.4 (9.5)	59.0 (11.7)	
Median (IQR)	61.0 (54.0-67.0)	60.5 (54.0-69.0)	64.0 (53.5-69.0)	60.0 (53.5-65.5)	61.0 (52.0-67.5)	
Range	26.0-79.0	20.0-89.0	44.0-81.0	36.0-79.0	21.0-78.0	
Preoperative KPS						<0.001[b]
<60	4/147 (2.7)	1/221 (0.5)	0/62 (0.0)	0/27 (0.0)	0/119 (0.0)	
60	15/147 (6.1)	1/221 (0.5)	0/62 (0.0)	1/27 (3.7)	0/119 (0.0)	
70	43/147 (29.3)	8/221 (3.6)	8/62 (12.9)	4/27 (14.8)	0/119 (0.0)	
80	61/147 (41.5)	66/221 (29.9)	15/62 (24.2)	12/27 (44.4)	12/119 (10.1)	
90	24/147	107/221 (48.4)	32/62 (51.6)	7/27 (25.9)	64/119 (55.8)	
100	0/147	38/221 (17.2)	7/62 (11.3)	3/27 (11.1)	43/119 (36.1)	
Median preoperative KPS (IQR)	80 (70-80)	90 (80-90)	90 (80-90)	80 (80-90)	90 (90-100)	
Preoperative ASA score						0.016[b]
I	18/143 (12.6)	29/215 (13.5)	12/62 (19.4)	10/27 (37.0)	18/116 (15.5)	
II	84/143 (58.7)	131/215 (60.9)	44/62 (71.0)	16/27 (59.3)	76/116 (65.5)	
III	37/143 (25.9)	53/215 (24.7)	6/62 (9.7)	1/27 (3.7)	22/116 (19.0)	
IV	4/143 (2.8)	2/215 (0.9)	0/62 (0.0)	0/27 (0.0)	0/116 (0.0)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-3)	2 (2-2)	2 (1-2)	2 (2-2)	
Preoperative NIHSS score						<0.001[b]
0	28/147 (19.0)	85/221 (38.4)	29/62 (46.8)	13/27 (48.1)	69/119 (58.0)	
1	42/147 (28.6)	68/221 (30.8)	15/62 (24.2)	6/27 (22.2)	34/119 (28.6)	
2	35/147 (23.8)	39/221 (17.6)	10/62 (16.1)	7/27 (25.9)	7/119 (5.9)	
3	15/147 (10.2)	17/221 (7.7)	4/62 (6.5)	0/27 (0.0)	6/119 (5.0)	
4	8/147 (5.4)	4/221 (1.8)	3/62 (4.8)	1/27 (3.7)	2/119 (1.7)	
>4	19/147 (12.9)	8/221 (3.6)	1/62 (1.6)	0/27 (0.0)	1/119 (0.8)	
Median preoperative NIHSS score (IQR)	2 (1-3)	1 (0-2)	1 (0-2)	1 (0-2)	0 (0-1)	

eTable 5: Summary data of the OFO subgroups – ΔKPS-EOR model at 6 months postoperatively (continued)

Characteristic	OFO 1a (n = 147)	OFO 1b (n = 221)	OFO 2 (n = 62)	OFO 3a (n = 27)	OFO 3b (n = 119)	*p* value
Tumor location by lobe Tumor location by lobe						0.50[b]
Frontal	42/147 (28.6)	69/221 (31.2)	23/60 (38.3)	10/27 (37.0)	36/119 (30.3)	
Parietal	43/147 (29.3)	59/221 (26.7)	12/60 ((20.0)	9/27 (33.3)	25/119 (21.0)	
Temporal	55/147 (37.4)	73/221 (33.0)	23/60 (38.3)	6/27 (22.2)	48/119 (3.4)	
Occipital	7/147 (4.8)	20/221 (9.0)	2/60 (3.3)	2/27 (7.4)	10/119 (8.4)	
Tumor location by hemisphere						0.41[b]
Left	81/147 (55.1)	137/221 (62.0)	39/61 (63.9)	13/27 (48.1)	67/119 (56.3)	
Right	66/147 (44.9)	84/221 (38.0)	22/61 (36.1)	14/27 (51.9)	52/119 (43.7)	
IDH status						0.069[b]
Wildtype	94/97 (96.9)	158/165 (95.8)	25/26 (96.2)	5/5 (100.0)	77/87 (88.5)	
Mutant	3/97 (3.1)	7/165 (4.2)	1/26 (3.8)	0/5 (0.0)	10/87 (11.5)	
MGMT status						0.91[b]
Methylated	43/105 (41.0)	61/148 (41.2)	12/25 (48.0)	4/9 (44.4)	29/78 (37.2)	
Unmethylated	62/105 (59.0)	87/148 (58.8)	13/25 (52.0)	5/9 (55.6)	49/78 (62.8)	
Mapping and surgical adjuncts						
Intraoperative electrophysiological mapping	19/147 (12.9)	54/221 (24.4)	2/62 (3.2)	0/27 (0.0)	31/119 (26.1)	<0.001[b]
Intraoperative ultrasound	26/147 (17.7)	26/221 (11.8)	5/62 (8.1)	0/27 (0.0)	15/119 (12.6)	0.16[b]
Intraoperative fluorescence	24/147 (16.3)	48/221 (21.2)	6/62 (9.7)	2/27 (7.4)	29/119 (24.4)	0.043[b]
Postoperative adjuvant therapy						NA
Radiotherapy only	0/147 (0.0)	0/221 (0.0)	0/62 (0.0)	0/27 (0.0)	0/119 (0.0)	
Chemotherapy only	0/147 (0.0)	0/221 (0.0)	0/62 (0.0)	0/27 (0.0)	0/119 (0.0)	
Both	147/147 (100.0)	221/221 (0.0)	62/62 (100.0)	27/27 (100.0)	119/119 (100.0)	
None	0/147 (0.0)	0/221 (0.0)	0.62 (0.0)	0/27 (0.0)	0/119 (0.0)	
Preoperative CE volume, ml						0.066[a]
Mean (SD)	65.7 (50.0)	51.7 (43.1)	55.4 (50.2)	54.6 (44.6)	51.7 (52.3)	
Median (Q1-Q3)	52.8 (28.0)	38.0 (20.1-69.1)	42.9 (21.2-64.9)	40.9 (22.8-89.3)	36.0 (15.3-68.5)	
Range	3.8-210.6	0.57-203.3	1.6-219.4	0.4-171.6	1.7-212.9	

eTable 5: Summary data of the OFO subgroups – ΔKPS-EOR model at 6 months postoperatively (continued)

Characteristic	OFO 1a (n = 147)	OFO 1b (n = 221)	OFO 2 (n = 62)	OFO 3a (n = 27)	OFO 3b (n = 119)	*p* value
Postoperative CE volume, ml						<0.001[a]
Mean (SD)	4.9 (8.0)	2.1 (4.1)	18.6 (17.0)	33.8 (26.5)	1.4 (4.1)	
Median (Q1-Q3)	2.1 (0.3-5.6)	0.4 (0.0-2.2)	14.3 (7.7-23.3)	25.0 (13.2-49.2)	0.0 (0.0-1.5)	
Range	0.0-44.7	0.0-35.8	0.6-93.7	0.2-94.6	0.0-41.0	
Extent of resection CE tumor, % by volume						<0.001[a]
Mean (SD)	93.1 (7.3)	96.0 (5.6)	65.3 (9.9)	35.0 (14.6)	97.5 (4.2)	
Median (Q1-Q3)	95.5 (89.3-99.2)	98.9 (93.3-100.0)	66.1 (58.1-72.3)	33.1 (26.7-48.4)	100 (96.8-100.0)	
Range	67.6-100.0	77.3-100.0	38.4-80.9	8.9-50.0	82.40-100.0	
Postoperative KPS at 6 months						<0.001[b]
<60	18/147 (12.2)	7/221 (3.2)	4/62 (6.5)	0/27 (0.0)	3/119 (2.5)	
60	14/147 (9.5)	7/221 (3.2)	5/62 (8.1)	3/27 (11.1)	10/119 (8.4)	
70	21/147 (14.3)	38/221 (17.2)	9/62 (14.5)	7/27 (25.9)	16/119 (13.4)	
80	51/147 (35.7)	71/221 (3.2)	13/62 (21.0)	11/27 (40.7)	34/119 (28.6)	
90	38/147 (25.9)	75/221 (33.9)	17/62 (27.4)	5/27 (18.5)	33/119 (27.8)	
100	5/147 (3.4)	23/221 (10.4)	4/62 (6.5)	1/27 (3.7)	23/119 (19.3)	
Median postoperative KPS at 6 months (IQR)	80 (70-90)	80 (80-90)	80 (70-90)	90 (80-90)	80 (80-90)	
ΔKPS[*]						<0.001[a]
Mean (SD)	14.1 (8.3)	-4.5 (5.0)	-18.1 (13.4)	4.1 (10.8)	-25.2 (8.5)	
Median (IQR)	10 (10-20)	0 (-10/0)	-10 (-30/-10)	0 (0-10)	-20 (-30/-20)	
Range	10-70	-10/10	-60/20	-10/30	-20/-60	
Median progression-free survival, months[±]	10.0 (7.5-11.0)	12.0 (11.0-14.0)	8.0 (6.0-9.0)	7.0 (6.0-12.5)	12.0 (10.5-16.5)	<0.001[c]
Median overall survival, months[±]	16.0 (14.0-19.0)	24.0 (21.0-30.5)	16.0 (12.0-22.0)	14.5 (12.5-22.0)	28.5 (23.5-41.5)	<0.001[c]

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 between the various OFO subgroups of the ΔKPS-EOR model at 6 weeks postoperatively using linear model ANOVA[a] and Pearson's chi-square test[b].

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing.

[*]With preoperative score as reference.

CHAPTER 10

Effect of awake craniotomy within eloquent glioblastoma subgroups (GLIOMAP): A propensity-score matched analysis of an international, multicenter, cohort study

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ABSTRACT

Background

Awake mapping has been associated with decreased neurological deficits and increased extent of resection in eloquent glioma resections. However, its effect within clinically relevant glioblastoma subgroups remains poorly understood. We aimed to assess the benefit of this technique in subgroups of patients with glioblastomas based on age, preoperative neurological morbidity, and Karnofsky Performance Score (KPS).

Methods

In this propensity score-matched analysis of an international, multicentre, cohort study (GLIOMAP), patients were recruited at four tertiary centres in Europe (Erasmus MC, Rotterdam and Haaglanden MC, The Hague, Netherlands, and UZ Leuven, Leuven, Belgium) and the USA (Brigham and Women's Hospital, Boston, MA). Patients were eligible if they were aged 18–90 years, undergoing resection, had a histopathological diagnosis of primary glioblastoma, their tumour was in an eloquent or near-eloquent location, and they had a unifocal enhancing lesion. Patients either underwent awake mapping during craniotomy, or asleep resection, as per treating physician or multidisciplinary tumour board decision. We used propensity-score matching (1:3) to match patients in the awake group with those in the asleep group to create a matched cohort, and to divide patients into subgroups stratified by age (<70 years vs ≥70 years), preoperative National Institute of Health Stroke Scale (NIHSS) score (score of 0–1 vs ≥2), and preoperative KPS (90–100 vs ≤80). We used Cox proportional hazard regressions to analyse the effect of awake mapping on the primary outcomes including postoperative neurological deficits (measured by deterioration in NIHSS score at 6 week, 3 months, and 6 months postoperatively), overall survival, and progression-free survival. We used logistic regression to analyse the predictive value of awake mapping and other perioperative factors on postoperative outcomes.

Findings

Between Jan 1, 2010, and Oct 31, 2020, 3919 patients were recruited, of whom 1047 with tumour resection for primary eloquent glioblastoma were included in analyses as the overall unmatched cohort. After propensity- score matching, the overall matched cohort comprised 536 patients, of whom 134 had awake craniotomies and 402 had asleep resection. In the overall matched cohort, awake craniotomy versus asleep resection resulted in fewer neurological deficits at 3 months (26 [22%] of 120 vs 107 [33%] of 323; p=0·019) and 6 months (30 [26%] of 115 vs 125 [41%] of 305; p=0·0048) postoperatively, longer overall survival (median 17·0 months [95% CI 15·0–24·0] vs 14·0 months [13·0–16·0]; p=0·00054), and longer progression-free survival (median 9·0 months [8·0–11·0] vs 7·3 months [6·0–8·8]; p=0·0060). In subgroup analyses, fewer postoperative neurological deficits occurred at 3

months and at 6 months with awake craniotomy versus asleep resection in patients younger than 70 years (3 months: 22 [21%] of 103 vs 93 [34%] of 272; p=0·016; 6 months: 24 [24%] of 101 vs 108 [42%] of 258; p=0·0014), those with an NIHSS score of 0–1 (3 months: 22 [23%] of 96 vs 97 [38%] of 254; p=0·0071; 6 months: 27 [28%] of 95 vs 115 [48%] of 239; p=0·0010), and those with a KPS of 90–100 (3 months: 17 [19%] of 88 vs 74 [35%] of 237; p=0·034; 6 months: 24 [28%] of 87 vs 101 [45%] of 223, p=0·0043). Additionally, fewer postoperative neurological deficits were seen in the awake group versus the asleep group at 3 months in patients aged 70 years and older (two [13%] of 16 vs 15 [43%] of 35; p=0·033; no difference seen at 6 months), with a NIHSS score of 2 or higher (3 months: three [13%] of 23 vs 21 [36%] of 58; p=0·040) and at 6 months in those with a KPS of 80 or lower (five [18%] of 28 vs 34 [39%] of 88; p=0·043; no difference seen at 3 months). Median overall survival was longer for the awake group than the asleep group in the subgroups younger than 70 years (19·5 months [95% CI 16·0–31·0] vs 15·0 months [13·0–17·0]; p<0·0001), an NIHSS score of 0–1 (18·0 months [16·0–31·0] vs 14·0 months [13·0–16·5]; p=0·00047 [A: OK?]), and KPS of 90–100 (19·0 months [16·0–31·0] vs 14·5 months [13·0–16·5]; p=0·00058 [A: OK?]). Median progression-free survival was also longer in the awake group than in the asleep group in patients younger than 70 years (9·3 months [95% CI 8·0–12·0] vs 7·5 months [6·5–9·0]; p=0·0061), in those with an NIHSS score of 0–1 (9·5 months [9·0–12·0] vs 8·0 months [6·5–9·0]; p=0·0035), and in those with a KPS of 90–100 (10·0 months [9·0–13·0] vs 8·0 months [7·0–9·0]; p=0·0010). No difference was seen in overall survival or progression-free survival between the awake group and the asleep group for those aged 70 years and older, with NIHSS scores of 2 or higher, or with a KPS of 80 or lower.

Interpretation

These data might aid neurosurgeons with the assessment of their surgical strategy in individual glioblastoma patients. These findings will be validated and further explored in the SAFE trial (NCT03861299) and the PROGRAM study (NCT04708171).

INTRODUCTION

Awake mapping can be employed by neurosurgeons during eloquent glioblastoma resections to help increase extent of resection while preventing potential neurological deficits in a safe and feasible manner. Indeed, this technique has been associated with improved outcomes in glioma patients, most notably neurological outcomes, functional and cognitive outcomes, radiological outcomes, and survival outcomes [1-19]. However, these studies included a mix of low-grade and high-grade glioma patients [1-14] or focused on glioblastoma patients as a whole [15-19]. Consequently, the impact of awake mapping within important subgroups of glioblastoma patients remains poorly understood which severely hampers the assessment of surgical strategies and indication setting of this technique in daily practice. Molinaro *et al* have shown that extending the tumor resection beyond the contrast-enhancing part of the tumor may improve survival outcomes in younger patients regardless of *IDH* or MGMT status, indicating that maximal resection of this non-contrast-enhancing part of the tumor may outweigh the negative prognostic implication of *IDH* wildtype status in these patients [20]. However, there is still a lack of understanding of the specific impact of awake mapping within clinical, rather than molecular subgroups of patients and its interplay with other potential predictive, prognostic and confounding factors. Gaining such an understanding would be essential for improving surgical decision making in these patients.

We aimed to advance the current literature by (1) comparing the surgical benefit of awake and asleep procedures in clinical subgroups of glioblastoma patients in terms of functional, neurological, radiological and survival outcomes; (2) evaluating the specific outcomes that awake mapping independently impacts within these patient subgroups. The results of this study may help neurosurgeons to select the optimal surgical strategy for individual glioblastoma patients.

METHODS

Study design and participants

This propensity-score matched analysis was done using an international cohort of patients admitted to four tertiary neurosurgical care institutes in the Netherlands (Erasmus MC, Rotterdam and Haaglanden MC, The Hague), Belgium (UZ Leuven, Leuven) and the USA (Brigham and Women's Hospital, Boston, MA). It was approved by the ethical committee of all centers and adhered to the Strengthening the Reporting of Observational studies in Epidemiology (known as STROBE) reporting guidelines. Patients were eligible if they were aged 18-90 years, had undergone resection, had a histopathological diagnosis of primary glioblastoma, their tumour was in an eloquent or near-eloquent location, and they had a

unifocal lesion. Exclusion criteria were multifocal or midline tumor location, grade II or III gliomas with malignant transformation, recurrent glioblastomas, or incompleteness of clinical data. We only included eloquent tumors to compare the awake and asleep technique in the appropriate setting. Whether or not the tumour was in an eloquent location was determined on the basis of preoperative MRI images using the Brodmann areas for the eloquent areas of motor function (area 4, 6 and 8), sensory function (area 1, 2 and 3), language function (area 22, 39, 40, 44 and 45) and visual function (area 17, 18 and 19). Due to the retrospective nature of this study, written informed consent was not required from patients.

Procedures

The surgical procedures regarding awake and asleep tumour resection are described in the appendix (pp 2–3). Surgical procedures were done by neurosurgeons at each site, as per local practice. After surgery, patients were transferred to the post-anaesthesia care unit, where each patient was haemodynamically and neurologically monitored for 24 h. A postoperative MRI-scan was performed within 72 h after the operation to assess residual tumour volume and extent of resection. Tumour volumes were assessed both preoperatively (within 24 h before resection) and postoperatively (within 72 h after resection) with volumetric measurements on T1-weighted post-gadolinium images based on the contrast-enhancing part of the tumour, which was certified by the radiology departments at each site. Postoperative T1-weighted post- gadolinium MRIs were compared with diffusion-weighted imaging sequences to exclude induced oedema or ischaemia in the tumour volumetrics. Patients were followed up at their respective neurosurgical outpatient clinics at 1 week and 6–8 weeks after the operation and with 2–6- month intervals at the neuro-oncological outpatient clinic, with neurological examination and an MRI. Neurolinguistic follow-up was done at 3 months postoperatively, consisting of Dutch Linguistic Intra- operative Protocol (DuLIP) subset tests, shortened Token Test, verbal fluency, Comprehensive Aphasia Test, and the Montreal Cognitive Assessment.

We collected data on patient demographics, preoperative functioning, comorbidities, tumor related factors (location by lobe and hemisphere), molecular factors (*IDH* status, MGMT status), surgical factors (intraoperative ultrasound, intraoperative fluorescence), vascular complications, adjuvant therapy, postoperative functioning (Karnofsky Performance Score [KPS] and National Institutes of Health [NIH] Stroke Scale [NIHSS] at 6 weeks, 3 months, and 6 months), volumetric tumor data and survival data.

Outcomes

The effects of awake mapping versus asleep mapping and a wide range of other perioperative factors were assessed for their effect on seven outcomes: postoperative neurological deficits (according to NIHSS score; loss of at least 1 point), postoperative KPS (loss of at least 10

points), extent of resection, residual tumour volume, receipt of adjuvant chemotherapy and radiotherapy, overall survival, and progression-free survival. Extent of resection was calculated as ([preoperative tumour volume – postoperative tumour volume]/preoperative tumour volume) × 100%. Overall survival was defined as the time from date of tumour resection until death, and progression -free survival was defined as the time from date of tumour resection until radiological recurrence of the tumour on T1-contrast MRI, last follow-up, or death, whichever occurred first. Patients were followed-up for progression-free survival and overall survival until death, last follow-up, or October, 2021 (end of data collection, 1 year after the last patient was enrolled).

Statistical analysis

Patients in the awake craniotomy group from the overall (unmatched) cohort were matched (1:3) with patients from the asleep resection group (using the *matchit* package in R—ie, nearest neighbour propensity -score matching) on the basis of various factors, which were sex (male vs female), age (continuous), preoperative KPS (continuous), preoperative NIHSS score (continuous), preoperative tumour volume (continuous), tumour location by lobe (frontal, vs parietal, vs temporal, occipital, vs insula, tumour location by hemisphere (right vs left), intraoperative fluorescence (yes vs no), year of surgery (continuous), study centre (Rotterdam, vs The Hague, vs Leuven, vs Boston), and adjuvant therapy with chemotherapy and radiotherapy (yes vs no). Next, to mimic a stratified randomisation design, we divided the original unmatched cohort into six subgroups according to age (<70 vs ≥70 years), preoperative NIHSS score (0–1 vs ≥2), and preoperative KPS (90–100 vs ≤80), and within these subgroups patients in the awake craniotomy group were matched (1:3) with patients from the asleep resection group on the basis of the aforementioned variables. We formed these six subgroups to translate clinically relevant subgroups of patients into a scientific setting as realistically as possible. Matching ratios for the overall cohort and subgroups were based on the number of patients included in the cohort and overall covariate balance based on the weighted standardised difference. In descriptive analyses of awake craniotomy versus asleep resection, we assessed the outcomes using the following timepoints and definitions: NIHSS deterioration at 6 weeks, 3 months, and 6 months postoperatively; KPS deterioration at 6 weeks, 3 months, and 6 months postoperatively; extent of resection at less than 72 h postoperatively; residual tumour volume at less than 72 h postoperatively; median overall survival; and median progression -free survival. Receipt of adjuvant treatment was not assessed as an outcome for the descriptive analysis, but was included in Cox proportional hazards regression and logistic regression analyses because it was a variable in the propensity-score matching. We summarised demographic cohort data using standard descriptive statistics. To test for differences between the unmatched and matched cohorts for categorical variables, we used Pearson's $\chi 2$ test. For continuous variables with two variables, we used the two- tailed Student's t test for independent groups. For continuous

variables with more than two groups, we used the one-way ANOVA test. We used multiple multivariable proportional hazard regressions to analyse the association (hazard ratios [HRs]) between awake craniotomy (independent variable X and the main exposure of the nearest-neighbour propensity- score matching) and each of the seven outcomes (dependent variables Y). We did these Cox proportional hazard regression analyses on the overall matched cohort and matched subgroups to minimise the risk of selection bias and confounding. Because including *IDH* mutation and MGMT methylation status in the matching procedure proved to be unstable as a result of missing data, we added these covariates to the Cox proportional hazards regression model to function as covariates in the study of the association between awake surgery and primary outcomes. In sensitivity analyses, we also added additional variables with a weighted standardised mean difference greater than 0·20 after matching to the Cox proportional hazards regression model. We tested the proportional hazards assumption using the cox.zph function (*survival* package in R) on the basis of the scaled Schoenfeld residuals. We did survival analyses using Kaplan -Meier estimates for overall survival and progression-free survival (*survival, survminer, dplyr,* and *ggplot2* packages in R). We analysed overall survival and progression-free survival for the overall matched cohorts and the six matched cohort subgroups. We stratified Kaplan-Meier curves for the overall matched cohort for *IDH* mutation status and MGMT methylation status and for MGMT methylation status in the case of crossing curves as a post-hoc analysis to adjust for non-proportional hazards. We tested significance between the survival times of different groups and subgroups using the log-rank test.

We used multiple multivariable logistic regressions to analyse the predictive value (odds ratios [ORs]) of various factors (independent variables X) on five of the seven outcomes (dependent variables Y): NIHSS score deterioration of at least 1 point at 6 weeks postoperatively (using preoperative score as reference); KPS score deterioration of at least 10 points at 6 weeks post- operatively (using preoperative score as reference); proportion of patients who had received no adjuvant chemotherapy and radiotherapy; absolute postoperative residual tumour volume in mL; and extent of resection as a percentage. For this logistic regression analysis, the independent variables X were study centre (Rotterdam, vs The Hague, vs Leuven, vs Boston), year of surgery (2010–15 vs 2016–20), sex (male vs female), age at diagnosis (continuous), preoperative KPS (90–100 vs ≤80), preoperative American Society of Anesthesiology score (score of 1, vs 2, vs 3, vs 4), preoperative NIHSSscore (0–1 vs ≥2), tumour location by lobe (frontal, vs parietal, vs temporal, vs occipital, vs insula), tumour location by hemisphere (right vs left), tumour location by eloquence (motor, sensory, language, vs visual), *IDH* mutation status (wildtype vs mutant), MGMT methylation status (methylated vs unmethylated), awake craniotomy (yes vs no), intraoperative ultrasound (yes vs no), intraoperative fluorescence (yes vs no), 6-week NIHSS deterioration (yes vs no), 6-week KPS deterioration (yes vs no), postoperative vascular complications (nominal), pre-

operative contrast-enhancing tumour volume (ordinal), postoperative contrast-enhancing tumour volume (ordinal), and extent of resection (ordinal). We addressed missing data for *IDH* and MGMT status using complete-case analysis, because these data were missing completely at random. We did these logistic regression analyses on the overall unmatched overall cohort and unmatched subgroups to identify potential predictors and to further test for effect modifiers while incorporating testing for interaction. We tested interaction using the formal test of effect × subgroup interaction. We considered all p values of less than 0·05 to be significant. We did all statistical analyses using R (version 4.1.0).

RESULTS

Between Jan 1, 2010, and Oct 31, 2020, 3919 patients with glioblastoma surgery were screened for eligibility and 1047 patients with primary glioblastoma resections in eloquent areas were enrolled (fifigure 1). Patient characteristics by institutional cohort (Erasmus MC, Rotterdam n=382; Haaglanden MC, The Hague n=354; UZ Leuven, Leuven n=111, Brigham and Women's Hospital, Boston, MA, n=200) are shown in table 1. The median age of participants at enrolment was 64 years (IQR 56·0–71·0), 404 (38·6%) were women and 643 (61·4%) were men. No data on race or ethnicity were collected. In the overall unmatched cohort (n=1047), patients who underwent awake resection differed significantly from patients who underwent awake craniotomy for multiple perioperative factors (table 2). After matching, these two groups were mostly comparable (table 2). Furthermore, patients in the awake and asleep groups were mostly comparable within all matched subgroups in terms of demographic, patient-related, and tumour -related factors (appendix pp 10–21). Results of the matching procedure are summarised in the appendix (p 32). Descriptive analyses of the matched cohorts indicated that a higher proportion of patients in the awake group than in the asleep group had NIHSS deterioration of 1 point or more at 3 months (26 [22%] of 120 patients in the awake group *vs* 107 [33%] of 323 in the asleep group; p=0·019) and 6 months postoperatively (30 [26%] of 115 *vs* 125 [41%] of 305; p=0·0048; table 2). There was no significant difference between the groups in 6-week NIHSS or KPS at 6 weeks, 3 months, or 6 months (table 2). Furthermore, in the awake group versus the asleep group, mean residual tumour volume was lower (1·9 mL [SD 5·6] *vs* 5·9 mL [11·0]; p<0·0001) and mean extent of resection was greater (95·4% [SD 8·4] *vs* 86·3% [19·3]; p<0·0001; table 2). Median overall survival was significantly longer in the awake group than in the asleep group (p=0·00054; table 2, fifigure 2A), as was median progression-free survival (p=0·0060; table 2, fifigure 3A). Kaplan-Meier plots of overall survival and progression-free survival after stratifying for *IDH* and MGMT status are shown in figure 2 and figure 3. Results of our sensitivity analyses are shown in the appendix (p 34).

Figure 1: Data Flow Diagram

Table 1: Demographic table for Erasmus MC Rotterdam, Haaglanden MC The Hague, UZ Leuven and BWH Boston Cohorts

Characteristic	Rotterdam Cohort (n = 382)	The Hague Cohort (n = 354)	Leuven Cohort (n = 111)	Boston Cohort (n = 200)	*p* value
Gender					0.037
Male	236/382 (61.2)	221/354 (62.4)	78/111 (70.3)	108/200 (54.0)	
Female	146/382 (38.2)	133/354 (37.6)	33/111 (29.7)	92/200 (46.0)	
Age at diagnosis, years					0.58
Mean (SD)	61.2 (10.9)	64.8 (11.1)	60.5 (11.8)	64.9 (11.8)	
Median (IQR)	62.5 (54-70)	67.0 (58.0-73.0)	64.0 (52.0-69.0)	66.0 (59.0-71.8)	
Range	22.0-82.0	25.0-89.0	20.0-85.0	23.0-90.0	
Preoperative KPS					<0.0001
<60	4/382 (1.0)	8/354 (2.3)	1/111 (0.9)	7/190 (3.7)	
60	19/382 (5.0)	23/354 (6.5)	2/111 (1.8)	7/190 (3.7)	
70	76/382 (19.9)	49/354 (13.8)	7/111 (6.3)	31/190 (16.3)	
80	122/382 (31.9)	105/354 (30.0)	26/111 (23.4)	58/190 (30.5)	
90	108/382 (28.3)	138/354 (39.0)	53/111 (47.7)	79/190 (41.6)	
100	53/382 (13.9)	31/354 (8.8)	22/111 (19.8)	8/190 (4.2)	
Median preoperative KPS (IQR)	80 (70-90)	80 (80-90)	90 (80-90)	80 (80-90)	
Preoperative ASA score					<0.0001
I	67/381 (17.6)	33/354 (9.3)	6/111 (5.4)	0/199 (0.0)	
II	257/381 (67.5)	244/354 (68.9)	52/111 (46.8)	36/199 (18.1)	
III	56/381 (14.7)	75/354 (21.2)	51/111 (45.9)	131/199 (65.8)	
IV	1/381 (0.3)	2/354 (0.6)	2/111 (1.8)	32/199 (16.1)	
Median preoperative ASA score (IQR)	2 (2-2)	2 (2-2)	2 (2-3)	2 (2-2)	
Preoperative NIHSS score					<0.0001
0	138/382 (36.1)	115/354 (32.5)	21/111 (18.9)	38/190 (20.0)	
1	125/382 (32.7)	95/354 (26.8)	28/111 (25.2)	61/190 (32.1)	
2	82/382 (21.5)	61/354 (17.2)	21/111 (18.9)	41/190 (21.6)	
3	19/382 (5.0)	31/354 (8.8)	14/111 (12.6)	22/190 (11.6)	
4	8/382 (2.1)	23/354 (6.5)	10/111 (9.0)	11/190 (5.8)	
>4	10/382 (2.6)	29/354 (8.2)	17/111 (15.3)	17/190 (8.9)	
Median preoperative NIHSS score (IQR)	1 (0-2)	1 (0-2)	2 (1-3)	1 (1-3)	

Table 1: Demographic table for Erasmus MC Rotterdam, Haaglanden MC The Hague, UZ Leuven and BWH Boston Cohorts (continued)

Characteristic	Rotterdam Cohort (n = 382)	The Hague Cohort (n = 354)	Leuven Cohort (n = 111)	Boston Cohort (n = 200)	*p* value
Tumor location by lobe					<0.0001
Frontal	120/382 (31.4)	118/354 (33.3)	33/111 (29.7)	73/200 (36.5)	
Parietal	84/382 (22.0)	95/354 (26.8)	34/111 (30.6)	43/200 (21.5)	
Temporal	152/382 (39.8)	126/354 (35.6)	26/111 (23.4)	68/200 (34.0)	
Occipital	26/382 (6.8)	15/354 (4.2)	18/111 (16.2)	16/200 (8.0)	
Tumor location by hemisphere					0.46
Left	219/382 (57.3)	176/354 (49.7)	65/111 (58.6)	121/200 (60.5)	
Right	163/382 (42.7)	178/354 (50.3)	46/111 (41.4)	79/200 (39.5)	
Tumor location by eloquence					0.0060
Motor	190/382 (49.7)	211/354 (59.6)	58/111 (52.3)	98/200 (49.0)	
Sensory	58/382 (15.2)	61/354 (17.2)	11/111 (9.9)	20/200 (10.0)	
Language	185/382 (48.4)	154/354 (43.5)	48/111 (43.2)	86/200 (43.0)	
Visual	79/382 (20.7)	61/354 (17.2)	30/111 (27.0)	16/200 (8.0)	
IDH status					<0.0001
Wildtype	157/164 (95.7)	248/286 (86.7)	88/93 (94.6)	188/197 (95.4)	
Mutant	7/164 (4.2)	38/286 (13.3)	5/93 (5.4)	9/197 (4.6)	
MGMT status					<0.0001
Methylated	99/189 (52.4)	93/344 (27.0)	10/29 (34.5)	102/190 (53.7)	
Unmethylated	90/189 (47.6)	251/344 (73.0)	19/29 (65.5)	88/190 (46.3)	
Mapping and surgical adjuncts					
Intraoperative mapping	41/382 (10.7)	24/354 (6.8)	27/111 (24.3)	48/200 (24.0)	<0.0001
Intraoperative ultrasound	73/382 (19.1)	0/354 (0.0)	0/111 (0.0)	90/200 (45.0)	<0.0001
Intraoperative fluorescence	25/382 (6.5)	17/354 (4.8)	110/111 (99.1)	3/200 (1.5)	<0.0001
Postoperative adjuvant therapy					<0.0001
Radiotherapy only	45/382 (11.8)	37/354 (10.5)	7/111 (6.3)	10/200 (5.0)	
Chemotherapy only	7/382 (1.8)	3/354 (0.8)	4/111 (3.6)	2/200 (1.0)	
Both	282/382 (73.8)	260/354 (73.4)	100/111 (87.4)	170/200 (85.0)	
None	48/382 (12.6)	54/354 (15.3)	3/111 (2.7)	18/200 (9.0)	

Table 1: Demographic table for Erasmus MC Rotterdam, Haaglanden MC The Hague, UZ Leuven and BWH Boston Cohorts (continued)

Characteristic	Rotterdam Cohort (n = 382)	The Hague Cohort (n = 354)	Leuven Cohort (n = 111)	Boston Cohort (n = 200)	*p* value
Reasons for no combined CTx + RTx					0.0020
Due to surgical deficits	25/100 (25.0)	20/94 (21.3)	0/14 (0.0)	0/30 (0.0)	
Due to rapid progression	25/100 (25.0)	15/94 (15.6)	3/14 (21.4)	2/30 (6.7)	
Pre-op already ineligible	28/100 (28.0)	50/94 (53.2)	8/14 (57.1)	12/30 (40.0)	
Patient's wish	17/100 (17.0)	4/94 (4.3)	1/14 (7.1)	6/30 (20.0)	
Due to inclusion in clinical trial	2/100 (2.0)	0/94 (0.0)	1/14 (7.1)	1/30 (3.33)	
Unknown	3/100 (3.0)	5/94 (5.3)	0/14 (0.0)	9/30 (30.0)	
6-week NIHSS-status, pre-op as ref					
Deteriorated	117/373 (31.4)	81/323 (25.1)	27/102 (26.5)	42/165 (25.5)	0.25
New	54/117 (46.2)	25/81 (30.9)	9/27 (33.3)	13/42 (30.9)	
Worsened	63/117 (53.8)	56/81 (69.1)	18/27 (66.7)	29/42 (68.1)	
Transient	13/117 (11.1)	15/81 (18.5)	7/27 (25.9)	10/42 (23.8)	
Permanent	68/117 (58.1)	31/81 (38.3)	19/27 (70.4)	32/42 (77.8)	
Unknown	36/117 (30.8)	35/81 (43.2)	1/27 (3.7)	0/42 (0.0)	
Improved	81/373 (21.7)	114/323 (35.3)	41/102 (40.2)	57/165 (34.5)	0.0010
Stable	175/373 (46.9)	128/323 (39.6)	34/102 (33.3)	66/165 (40.0)	0.56
3-month NIHSS-status, pre-op as ref					
Deteriorated	113/290 (39.0)	61/219 (27.9)	34/100 (34.0)	40/152 (26.3)	0.015
New	54/113 (47.8)	29/61 (47.5)	13/34 (38.2)	14/40 (35.0)	
Worsened	59/113 (52.2)	32/61 (52.5)	21/34 (61.8)	26/40 (65.0)	
Improved	56/290 (19.3)	79/219 (50.0)	34/100 (34.0)	57/152 (37.5)	<0.0001
Stable	121/290 (41.7)	79/219 (50.0)	32/100 (32.0)	55/152 (36.2)	0.29
6-month NIHSS-status, pre-op as ref					
Deteriorated	124/268 (46.3)	66/189 (34.9)	35/96 (36.5)	42/137 (30.7)	0.009
New	64/125 (51.2)	33/66 (50.0)	13/35 (37.1)	16/42 (38.1)	
Worsened	61/125 (48.8)	33/66 (50.0)	22/35 (62.9)	26/42 (61.9)	
Improved	47/268 (17.5)	58/189 (30.7)	36/96 (37.5)	58/137 (42.3)	<0.0001
Stable	97/268 (36.2)	65/189 (34.4)	25/96 (26.0)	37/137 (27.0)	0.13

Table 1: Demographic table for Erasmus MC Rotterdam, Haaglanden MC The Hague, UZ Leuven and BWH Boston Cohorts (continued)

Characteristic	Rotterdam Cohort (n = 382)	The Hague Cohort (n = 354)	Leuven Cohort (n = 111)	Boston Cohort (n = 200)	*p* value
Postoperative vascular complications					
None	271/374 (89.0)	258/344 (90.1)	100/106 (94.3)	196/199 (98.5)	<0.0001
Major ischemia	23/374 (6.1)	16/344 (4.7)	3/106 (2.8)	3/199 (1.5)	0.061
Rebleed	18/374 (4.8)	15/344 (4.4)	3/106 (2.8)	0/199 (0.0)	0.050
Preoperative CE tumor volume, ml					<0.0001
Mean (SD)	59.5 (52.5)	78.5 (57.3)	32.6 (22.6)	45.7 (44.6)	
Median (Q1-Q3)	45.1 (24.3-80.8)	63.3 (35.8-119.3)	29.2 (14.3-49.8)	29.7 (11.0-66.5)	
Range	0.4-237.0	0.7-237.6	0.75-113.2	1.1-225.7	
Postoperative CE tumor volume, ml					<0.0001
Mean (SD)	7.4 (14.7)	6.0 (12.2)	0.95 (3.3)	2.2 (2.3)	
Median (Q1-Q3)	2.1 (0.3-6.8)	1.8 (0-5.7.0)	2.9 (1.4-5.0)	1.6 (0.0-1.4)	
Range	0.0-94.0	0.0-93.7	0.0-26.4	0.0-14.9	
Extent of resection CE tumor, % by volume					<0.0001
Mean (SD)	90.0 (12.8)	91.6 (13.6)	94.0 (9.7)	93.4 (6.3)	
Median (Q1-Q3)	94.3 (85.9-98.6)	97.1 (88.4-100.0)	97.6 (94.0-99.0)	98.0 (95.48-100.0)	
Range	8.9-100.0	9.0-100.0	54.5-100.0	48.2-100.0	
Median progression-free survival, months (95% CI)	6.0 (3.0-10.0)	12.0 (4.0-25.5)	10.5 (6.0-15.75)	7.0 (4.0-12.0)	<0.0001
Median overall survival, months (95% CI)	11.0 (6.0-17.9)	15.5 (5.5-28.0)	16.0 (11.0-23.5)	12.0 (5.0-22.5)	<0.0001

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 between the Erasmus MC, Haaglanden MC, UZ Leuven and Brigham and Women's Hospital cohorts. Abbreviations: CI: confidence interval; CE: contrast-enhancing; CTx: chemotherapy; RTx: radiotherapy; SD: standard deviation; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase.

Table 2: Patient characteristics of the unmatched and matched overall cohorts

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	**Asleep resection (n = 907)**	***p* value**	**Awake craniotomy (n = 134)**	**Asleep resection (n = 402)**	***p* value**
Center			<0.0001			<0.0001
Rotterdam	44/140 (31.4)	338/907 (37.3)		44/134 (32.8)	178/402 (44.3)	
The Hague	24/140 (17.1)	330/907 (36.4)		24/134 (17.9)	139/402 (34.6)	
Leuven	27/140 (19.3)	84/907 (9.3)		27/134 (20.1)	65/402 (16.2)	
Boston	45/140 (32.1)	155/907 (17.1)		39/134 (29.1)	20/402 (5.0)	
Year of surgery			0.032			0.00037
2010-2015	46/140 (32.9)	221/907 (24.4)		42/134 (31.3)	197/402 (49.0)	
2016-2020	94/140 (67.1)	686/907 (75.6)		92/134 (68.9)	205/402 (51.0)	
Gender			0.19			0.874
Male	93/140 (66.4)	550/907 (60.6)		90/134 (67.2)	265/402 (65.9)	
Female	47/140 (33.7)	357/907 (39.4)		44/134 (32.8)	137/402 (34.1)	
Age at diagnosis, years			<0.0001			0.12
Mean (SD)	57.5 (13.5)	63.9 (10.8)		57.5 (12.7)	61.1 (11.2)	
Median (IQR)	59.0 (50.0-67.3)	65.0 (57.0-72.0)		59.0 (49.3-66.8)	62.0 (54.0-70.0)	
Range	22.0-87.0	20.0-90.0		22.0-87.0	20.0-87.0	
Preoperative KPS			<0.0001			0.072
<60	1/140 (0.7)	19/907 (2.1)		1/134 (0.7)	0/402 (0.0)	
60	1/140 (0.0)	50/907 (5.5)		1/134 (0.7)	1/402 (0.2)	
70	6/140 (4.3)	157/907 (17.3)		6/134 (4.5)	31/402 (7.7)	
80	27/140 (19.3)	283/907 (31.2)		27/134 (20.1)	112/402 (27.9)	
90	65/140 (46.4)	313/907 (34.5)		65/134 (48.5)	191/402 (47.5)	
100	40/140 (28.6)	104/907 (11.5)		34/134 (25.4)	67/402 (16.7)	
Median preoperative KPS (IQR)	90 (80-100)	80 (80-90)		90 (80-100)	90 (80-90)	

Table 2: Patient characteristics of the unmatched and matched overall cohorts (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	Asleep resection (n = 907)	*p* value	Awake craniotomy (n = 134)	Asleep resection (n = 402)	*p* value
Preoperative ASA score			0.37			0.014
I	17/123 (13.8)	89/902 (9.9)		17/119 (14.3)	61/401 (15.2)	
II	64/123 (52.0)	524/902 (58.1)		63/119 (52.9)	262/401 (65.3)	
III	40/123 (32.5)	273/902 (30.3)		39/119 (32.8)	75/401 (18.5)	
IV	1/123 (0.8)	16/902 (1.8)		0/119 (0.0)	3/401 (0.7)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-3)		2 (2-3)	2 (1-2)	
Preoperative NIHSS score			<0.0001			0.31
0	63/134 (47.0)	249/903 (27.6)		63/134 (47.0)	160/402 (39.8)	
1	44/134 (32.8)	267/903 (29.6)		44/134 (32.8)	122/402 (30.3)	
2	17/134 (12.7)	188/903 (20.8)		17/134 (12.7)	72/402 (17.9)	
3	3/134 (2.2)	83/903 (9.2)		3/134 (2.2)	20/402 (5.0)	
4	4/134 (3.0)	48/903 (5.3)		4/134 (3.0)	13/402 (3.2)	
>4	3/134 (2.2)	68/903 (7.5)		3/134 (2.2)	15/402 (3.7)	
Median preoperative NIHSS score (IQR)	0 (0-1)	1 (0-2)		0 (0-1)	1 (0-2)	
Tumor location by lobe			0.012			0.055
Frontal	54/140 (38.6)	289/905 (31.9)		51/134 (38.1)	135/401 (33.7)	
Parietal	34/140 (24.3)	221/905 (24.4)		33/134 (24.6)	102/401 (25.4)	
Temporal	49/140 (35.0)	314/905 (34.7)		47/134 (35.1)	140/401 (34.9)	
Occipital	1/140 (0.7)	73/905 (8.1)		1/134 (0.7)	24/401 (6.0)	
Insula	2/140 (1.4)	8/905 (0.9)		2/134 (1.5)	0/401 (0.0)	
Tumor location by hemisphere			<0.0001			0.086
Left	112/140 (80.0)	438/907 (48.3)		108/134 (80.6)	292/402 (72.6)	
Right	28/140 (20.0)	469/907 (51.7)		26/134 (19.4)	110/402 (27.4)	
Tumor location by eloquence			<0.0001			<0.00021
Motor	64/140 (45.7)	493/904 (54.5)		61/134 (45.5)	190/402 (47.3)	
Sensory	10/140 (7.1)	98/904 (10.8)		10/134 (7.5)	27/402 (6.7)	
Language	92/140 (65.7)	385/904 (42.6)		82/134 (61.2)	219/402 (54.5)	
Visual	3/140 (2.1)	167/904 (18.5)		3/134 (2.2)	75/402 (18.7)	

Table 2: Patient characteristics of the unmatched and matched overall cohorts (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	Asleep resection (n = 907)	*p* value	Awake craniotomy (n = 134)	Asleep resection (n = 402)	*p* value
IDH status			0.52			0.68
Wildtype	107/118 (90.7)	574/621 (92.4)		101/112 (90.2)	234/254 (92.1)	
Mutant	11/118 (9.3)	47/621 (7.6)		11/112 (9.8)	20/254 (7.9)	
MGMT status			0.14			0.070
Methylated	45/95 (47.4)	259/657 (39.4)		42/89 (47.2)	80/248 (32.3)	
Unmethylated	50/95 (52.6)	398/657 (60.5)		57/89 (64.4)	169/248 (68.3)	
Surgical adjuncts						
Intraoperative ultrasound	29/140 (20.7)	133/907 (14.7)	0.065	28/134 (20.9)	43/402 (10.7)	0.0826
Intraoperative fluorescence	29/140 (20.7)	126/907 (13.9)	0.093	29/134 (21.6)	74/402 (18.4)	0.81
Postoperative adjuvant therapy			0.013			0.279
Radiotherapy only	7/140 (5.0)	91/907 (10.0)		3/134 (2.2)	27/398 (6.7)	
Chemotherapy only	3/140 (2.1)	13/907 (1.4)		3/134 (2.2)	4/398 (1.0)	
Chemoradiotherapy	122/140 (87.1)	685/907 (75.5)		122/134 (91.0)	341/398 (85.0)	
None	8/140 (5.7)	115/907 (12.7)		6/134 (4.5)	26/398 (6.5)	
Reasons for no combined CTx + RTx			<0.0001			0.693
Due to surgical deficits	1/18 (5.6)	33/219 (15.1)		1/12 (8.3)	9/57 (15.8)	
Due to rapid progression	3/18 (16.7)	30/219 (13.7)		2/12 (16.7)	6/57 (10.5)	
Pre-op already ineligible	6/18 (33.3)	113/219 (51.6)		6/12 (50.0)	28/57 (49.1)	
Patient's wish	2/18 (11.1)	26/219 (11.9)		1/12 (8.3)	10/57 (17.5)	
Due to inclusion in clinical trial	3/18 (16.7)	3/219 (1.4)		1/12 (8.3)	2/57 (3.5)	
Unknown	3/18 (16.7)	14/219 (6.4)		1/12 (8.3	2/57 (3.5)	

Table 2: Patient characteristics of the unmatched and matched overall cohorts (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	Asleep resection (n = 907)	*p* value	Awake craniotomy (n = 134)	Asleep resection (n = 402)	*p* value
6-week NIHSS-status, pre-op as ref						
Deteriorated	25/128 (19.5)	219/837 (26.2)	0.11	27/125 (21.6)	99/386 (25.6)	0.20
New	12/25 (48.0)	84/219 (38.4)		12/27 (44.4)	45/99 (45.4)	
Worsened	13/25 (52.0)	135/219 (61.6)		15/27 (55.6)	54/99 (54.5)	
Transient	9/25 (36.0)	58/219 (26.5)		11/27 (40.7)	8/99 (8.1)	
Permanent	16/25 (64.0)	161/219 (73.5)		16/27 (59.3)	91/99 (91.9)	
Improved	35/128 (27.3)	267/837 (31.9)	0.30	36/125 (28.9)	115/386 (29.8)	0.83
Stable	68/128 (53.1)	351/837 (41.9)	0.0067	62/125 (49.6)	186/386 (44.6)	0.78
6-week KPS-status, pre-op as ref						
Deteriorated	46/128 (35.9)	317/848 (37.4)	0.75	46/128 (35.9)	155/391 (39.6)	0.46
Improved	27/128 (21.1)	331/848 (39.0)	<0.0001	27/128 (21.1)	76/391 (19.4)	0.68
Stable	55/128 (43.0)	200/848 (23.6)	<0.0001	55/128 (43.0)	160/391 (40.9)	0.68
3-month NIHSS-status, pre-op as ref						
Deteriorated	25/128 (19.5)	202/641 (31.5)	0.0072	26/120 (21.7)	107/323 (33.1)	0.019
New	13/25 (52.0)	90/202 (42.5)		13/26 (50.0)	53/107 (49.5)	
Worsened	12/25 (48.0)	112/202 (55.4)		13/26 (50.0)	54/107 (50.5)	
Improved	39/128 (30.5)	192/641 (30.0)	0.91	36/120 (30.0)	82/323 (25.4)	0.33
Stable	64/128 (50.0)	202/641 (38.5)	<0.001	58/120 (48.3)	134/323 (41.5)	0.20
3-month KPS-status, pre-op as ref						
Deteriorated	46/119 (38.7)	253/647 (39.1)	0.93	46/119 (38.7)	139/324 (42.9)	0.42
Improved	21/119 (17.6)	253/647 (39.1)	<0.0001	21/119 (17.6)	65/324 (20.1)	0.57
Stable	52/119 (44.0)	141/647 (21.8)	<0.0001	52/119 (43.7)	120/324 (37.0)	0.20
6-month NIHSS-status, pre-op as ref						
Deteriorated	30/115 (26.1)	216/575 (37.6)	0.019	30/115 (26.1)	125/305 (41.0)	0.0048
New	16/30 (53.3)	102/216 (47.2)		16/30 (53.3)	67/161 (41.6)	
Worsened	14/30 (46.7)	114/216 (52.8)		14/30 (46.7)	94/161 (58.4)	
Improved	33/115 (28.7)	166/575 (20.2)	0.97	33/115 (28.7)	71/305 (23.3)	0.36
Stable	52/115 (45.2)	193/575 (33.6)	0.017	52/115 (45.2)	109/325 (33.5)	0.025

Table 2: Patient characteristics of the unmatched and matched overall cohorts (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	Asleep resection (n = 907)	*p* value	Awake craniotomy (n = 134)	Asleep resection (n = 402)	*p* value
6-month KPS-status, pre-op as ref						
Deteriorated	51/117 (43.6)	261/579 (45.1)	0.77	51/117 (43.6)	152/300 (50.7)	0.19
Improved	19/117 (16.2)	206/579 (35.6)	<0.0001	19/117 (16.2)	52/300 (17.3)	0.79
Stable	47/117 (40.2)	112/579 (19.3)	<0.0001	47/119 (39.5)	96/300 (32.0)	0.14
Postoperative vascular complications						
None	134/138 (97.1)	816/864 (94.4)	0.19	103/132 (78.0)	312/392 (79.6)	0.70
Major ischemia	3/138 (2.2)	29/864 (3.4)	0.46	2/132 (1.5)	11/392 (2.8)	0.41
Postoperative (reactive) bleeding	1/138 (0.7)	19/864 (2.2)	0.25	1/132 (0.8)	7/392 (1.8)	0.40
Preoperative CE tumor volume, ml			<0.0001			0.19
Mean (SD)	42.1 (50.0)	61.7 (51.9)		38.2 (46.8)	41.2 (36.6)	
Median (Q1-Q3)	26.4 (11.6-54.5)	49.4 (25.1-87.8)		22.4 (11.0-48.0)	24.5 (17.1-68.0)	
Range	0.8-208.0	0.4-396.0		0.8-208.0	0.4-334.7	
Postoperative CE tumor volume, ml			<0.0001			<0.0001
Mean (SD)	2.2 (6.1)	7.6 (1.6)		1.9 (5.6)	5.9 (11.0)	
Median (Q1-Q3)	0.1 (0.0-1.6)	1.8 (0.0-6.8)		0.0 (0.0-1.3)	1.5 (0.0-5.8)	
Range	0.0-41.0	00-164.0		0.0-41.0	0.0-81.7	
Extent of resection CE tumor, % by volume			<0.0001			<0.0001
Mean (SD)	95.5 (8.2)	87.6 (18.2)		95.4 (8.4)	86.3 (19.3)	
Median (Q1-Q3)	99.8 (94.8-100.0)	95.3 (83.6-100.0)		99.8 (94.4-100.0)	95.2 (81.3-100.0)	
Range	48.2-100.0	21.0-100.0		48.2-100.0	21.0-100.0	
Median progression-free survival, months (95% CI)	9.0 (15.5-19.0)	7.0 (3.5-15.0)	0.31	9.0 (8.0-11.0)	7.3 (6.0-8.75)	0.0060
Median overall survival, months (95% CI)	15.0 (10.0-30.8)	12.5 (6.0-23.5)	0.0010	17.0 (15.0-24.0)	14.0 (13.0-16.0)	<0.00054

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the unmatched and matched awake-asleep cohorts.

Abbreviations: CI: confidence interval; CE: contrast-enhancing; CTx: chemotherapy; RTx: radiotherapy; SD: standard deviation; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase.

The effect of awake mapping versus asleep resection was assessed within the matched subgroups. The first two subgroups consisted of patients younger than 70 years (114 [85%] of 134 in the awake craniotomy group, 342 [85%] of 402 in the asleep resection group) and aged 70 years and older (20 [15%] in the awake craniotomy group and 60 [15%] in the asleep resection group. Among the patients younger than 70 years, a lower proportion in the awake group than in the asleep group had NIHSS deterioration of at least 1 point at 3 months (p=0·016) and at 6 months postoperatively (p=0·0014; appendix pp 10–13). No significant differences between the groups were found for NIHSS deterioration at 6 weeks or KPS deterioration at 6 weeks, 3 months, or 6 months postoperatively (appendix pp 10–13). Like the overall cohort, mean residual tumour volume was lower (p<0·0001) and extent of resection was greater (p<0·0001) in the awake group than in the asleep group (appendix pp 10–13). Median overall survival was significantly longer in the awake group than in the asleep group (figure 2), as was progression-free survival (figure 3). Among patients aged 70 years and older, the proportion of patients who had 3-month NIHSS deterioration was lower in the awake group than in the asleep group (p=0·033), 6-month KPS deterioration was higher (p<0·0001), and extent of resection was greater in the awake group than in the asleep group (p=0·036). No significant differences were found between the awake and asleep groups in NIHSS deterioration at 6 weeks and 6 months; KPS deterioration at 6 weeks or 3 months; overall survival; or progression-free survival (figure 2, 3; appendix pp 10-13). The third and fourth subgroups consisted of patients with a preoperative NIHSS score of 0-1 (107 [80%] of 134 in the awake craniotomy group and 321 [80%] of 402 in the asleep resection group) and of 2 or higher (27 [20%] in the awake group and 81 [20%] in the asleep group; appendix pp 14–17). Among those with a preoperative NIHSS score of 0–1, a lower proportion of patients in the awake group than in the asleep group had NIHSS deterioration of at least 1 point at 3 months (p=0·0071) and 6 months postoperatively (p=0·0010) no difference was seen at 6 weeks (p=0·11). No differences in KPS deterioration was seen at 6 weeks, 3 months, or 6 months (appendix pp 14–17). Lower mean residual tumour volume (p<0·0001) and a greater extent of resection (p<0·0001) were seen in the awake group than in the asleep group (appendix pp 14–17). Additionally, patients in the awake group versus the asleep group had a significantly longer overall survival (18·0 months [95% CI 16·0–31·0] *vs* 14·0 months [13·0–16·5]; p=0·00047) and progression-free survival (9·5 months [95% CI 9·0–12·0] *vs* 8·0 months [6·5–9·0]; p=0·0035; appendix pp 6, 8, 14–17). In the subgroup of patients with a preoperative NIHSS score of 2 or higher, a lower proportion of patients in the awake group than in the asleep group had with NIHSS deterioration at 3 months (p=0·040) no difference was seen at 6 weeks (p=0·91) or 6 months p=0·24). No significant difference was seen between the groups in KPS deterioration at 6 weeks, 3 months, or 6 months. Mean residual volume was lower (p=0·048) and extent of resection was greater in the awake group than in the asleep group (p=0·048). We found no significant differences between the awake and

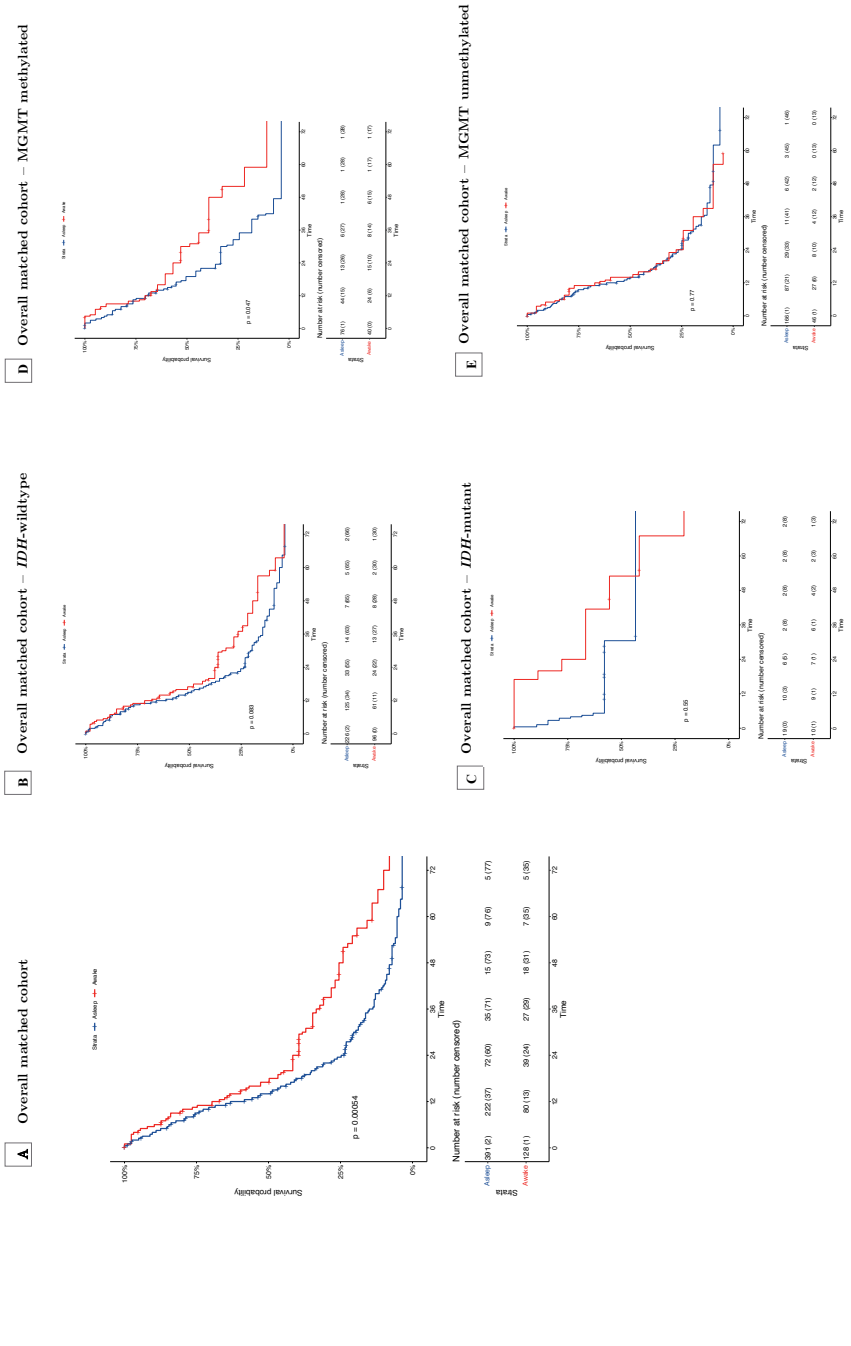

Figure 2: Kaplan-Meier curves for Overall Survival

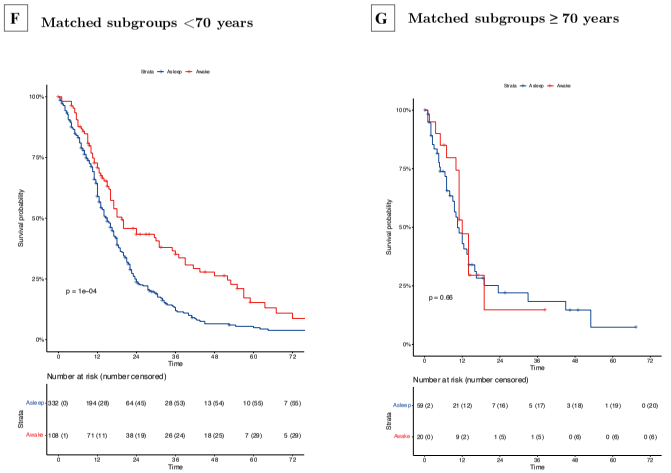

Figure 2: Kaplan-Meier curves for Overall Survival (continued)

Data are shown for the overall matched cohort (A), the overall match cohort by IDH mutation status (B, C) and MGMT methylation status (D, E), and in the matched subgroups by age (F, G). A: median OS for the awake group (n=134, 90 events) was 17.0 months (95% CI 15.0-24.0) versus 14.0 months (95% CI 13.0-16.0) for the asleep group (n=402, 310 events). B: median OS for the awake group (n=101, 65 events) was 17.0 months (95% CI 14.0-24.0) versus 15.0 months (95% CI 13.0-17.0) for the asleep group (n=234, 159 events). C: median OS for the awake group (n=11, 6 events) was 53.0 months (95% CI 24.0-NA) versus 30.5 months (95% CI 4.5-NA) for the asleep group (n=20, 9 events). D: median OS for the awake group (n=42, 22 events) was 30 months (95% CI 16.0-Inf) versus 19.0 months (95% CI 14.5-30.0) for the asleep group (n=80, 47 events). E: median OS for the awake group (n=57, 33 events) was 14.0 months (95% CI 12.5-23.0) versus 14.0 months (95% CI 12.0-16.0) for the asleep group (n=169, 119 events). F: median OS for the awake group (n=114, 76 events) was 19.5 months (95% CI 16.0-31.0) versus 15.0 months (95% CI 13.0-17.0 months) for the asleep group (n=342, 271 events). G: median OS for the awake group (n=20, 14 events) was 12.0 months (95% CI 11.0-NA) versus 10.5 months (95% CI 9.0-16.0) for the asleep group (n=60, 39 events). Groups are described in table 2 and in the appendix (pp 10-13). Kaplan-Meier curves for overall survival of matched subgroups by preoperative NIHSS score and KPS are shown in the appendix (pp 6–7). KPS=Karnofsky Performance Score. NIHSS=National Institute of Health Stroke Scale.

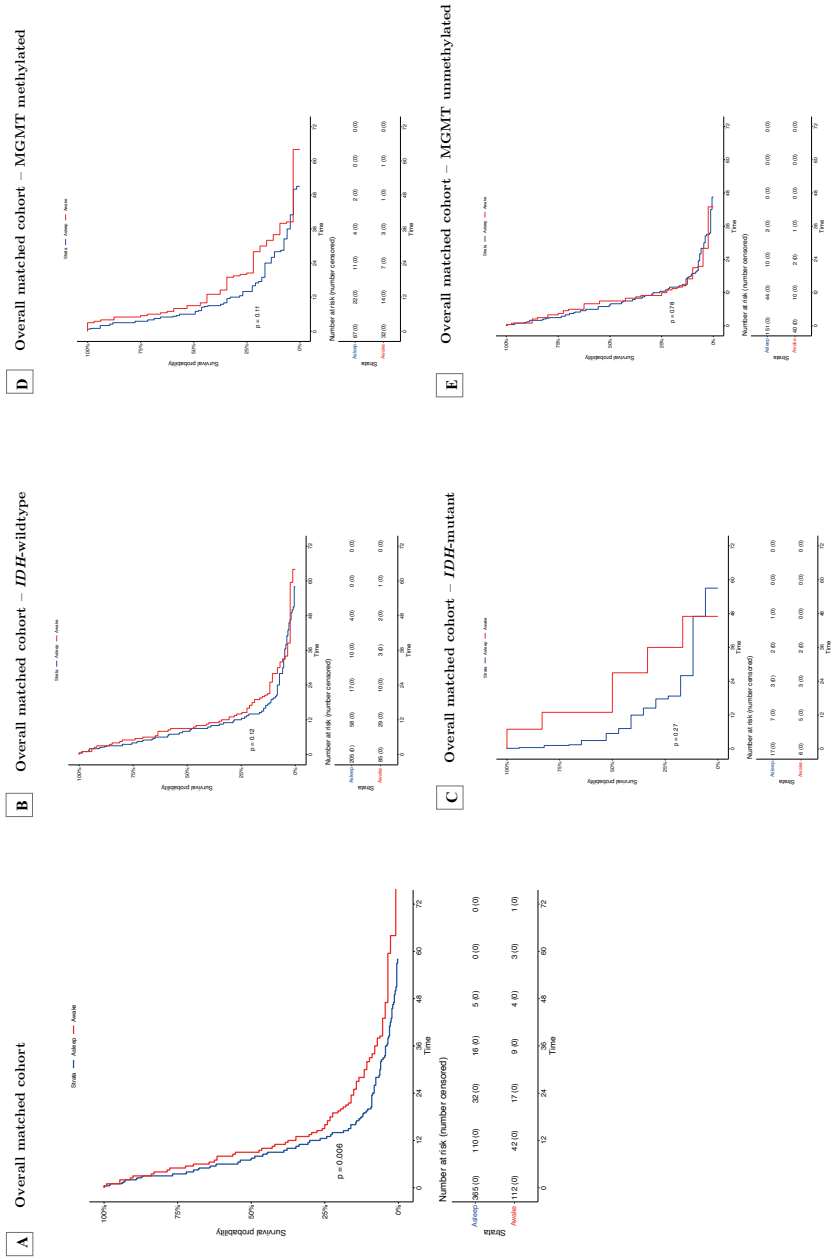

Figure 3: Kaplan-Meier curves for Progression-Free Survival

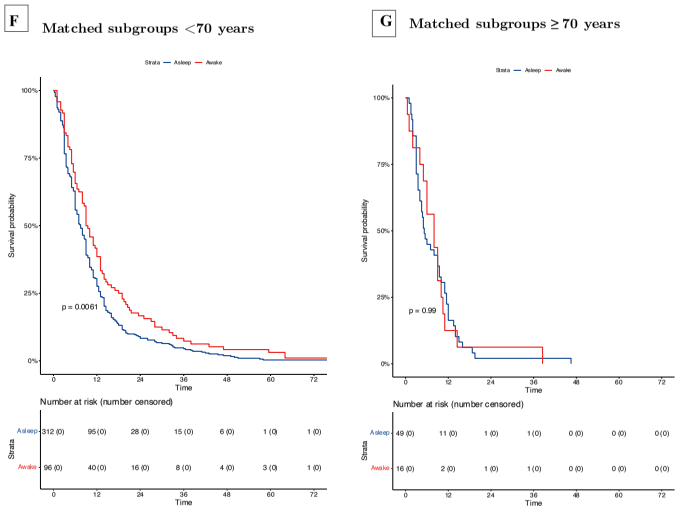

Figure 3: Kaplan-Meier curves for Progression-Free Survival (continued)

Data are shown for the overall matched cohort (A), the overall match cohort by IDH mutation status (B, C) and MGMT methylation status (D, E), and in the matched subgroups by age (F, G). A: median PFS for the awake group (n=112, 112 events) was 9.0 months (95% CI 8.0-11.0) versus 7.3 months (95% CI 6.0-8.75) for the asleep group (n=365, 365 events). B: median PFS for the awake group (n=85, 85 events) was 9.0 months (95% CI 8.0-11.0) versus 8.0 months (95% CI 7.0-9.0) for the asleep group (n=205, 205 events). C: median PFS for the awake group (n=6, 6 events) was 20.0 months (95% CI 13.0-Inf) versus 5.5 months (95% CI 1.5-18.8) for the asleep group (n=17, 17 events). D: median PFS for the awake group (n=32, 32 events) was 9.0 months (95% CI 6.5-19.5) versus 6.0 months (95% CI 5.0-9.5) for the asleep group (n=67, 67 events). E: median PFS for the awake group (n=40, 40 events) was 9.0 months (95% CI 6.0-11.0) versus 7.5 months (95% CI 6.0-9.0) for the asleep group (n=151, 151 events). F: median PFS for the awake group (n=96, 96 events) was 9.3 months (95% CI 8.0-12.0) versus 7.5 months (95% CI 6.5-9.0 months) for the asleep group (n=312, 312 events). G: median PFS for the awake group (n=16, 16 events) was 8.0 months (5.0-11.0) versus 5.3 months (95% CI 4.0-9.5) for the asleep group (n=49, 49 events). Groups are described in table 2 and in the appendix (pp 10-13). Kaplan-Meier curves for progression-free survival of matched subgroups for preoperative NIHSS and KPS are shown in the appendix (pp 8–9). KPS=Karnofsky Performance Score. NIHSS=National Institute of Health Stroke Scale.

asleep patients in this subgroup for overall survival and progression-free survival (appendix pp 6, 8, 14–17).

The fifth and sixth subgroups consisted of patients with a preoperative KPS of 90–100 (99 [74%] of 134 patients in the awake craniotomy group and 297 [74%] of 402 in the asleep resection group) and of 80 or less (35 [26%] in the awake group and 105 [26%] in the asleep group; appendix pp 18–21). Similar to the patients in the NIHSS 0–1 subgroup, among patients in the KPS 90–100 subgroup a lower proportion of patients in the awake group than in the asleep group had NIHSS deterioration at 3 months (p=0·034) and 6 months postoperatively (p=0·0043); no difference was seen at 6 weeks (p=0·19). Also, a lower proportion of patients in the awake group than in the asleep group had KPS deterioration at 3 months (p=0·027) and 6 months (p=0·017); No difference was seen in KPS deterioration at 6 weeks (appendix pp 18–21. Patients in the awake group had a lower mean residual tumour volume (p<0·0001) and a greater extent of resection (p<0·0001) than did those in the asleep group. Moreover, patients in the awake group had a significantly longer overall survival (19·0 months [95% CI 16·0–31·0] *vs* 14·5 months [13·0–16·5]; p=0·00058) and progression-free survival (10·0 months [95% CI 9·0–13·0] *vs* 8·0 months [7·0–9·0]; p=0·0010) than did those in the asleep group (appendix pp 7, 9, 18–21). Among patients with a KPS of 80 or lower, a lower proportion of those in the awake group than in the asleep group had NIHSS deterioration at 6 months postoperatively (p=0·043). Patients in the awake group had a lower mean residual tumour volume (p=0·0064) and a greater extent of resection (p=0·014) than did those in the asleep group. No significant differences were found between the awake and asleep groups for 6-week and 3-month NIHSS, KPS at 6 weeks, 3 months, and 6 months, overall survival, and progression-free survival (appendix pp 7, 9, 18–21). Testing for association between awake craniotomy and the five prespecified outcomes using multiple multi- variable Cox proportional hazard regression analyses for the matched overall cohorts indicated awake craniotomy as an independent factor for gross total resection based on 0·0–0·2 mL residual tumour volume (p=0·013), gross total resection based on 98–100% extent of resection (p=0·038), and overall survival (p=0·048; appendix p 33). In the overall cohort, NIHSS deterioration, KPS deterioration, adjuvant therapy, and progression-free survival were not significantly associated with awake mapping; results for each matched subgroup are in the appendix (p 33). Schoenfeld residuals for all Cox pro- portional hazards models were not significant, indicating no violation of the proportional-hazards assumption (data not shown). The association of awake craniotomy with primary outcomes was assessed using predictive testing with multiple multivariable logistic regression analyses based on the unmatched cohorts. Overall, awake craniotomy was independently associated with gross total resection based on 0·0–0·2 mL residual tumour volume (p=0·013) and gross total resection based on 98–100% extent of resection (p=0·0030; appendix pp 22–31). For the overall unmatched cohort, awake craniotomy was not associated with receipt of adju-

vant therapy (p=0·44), 6-week KPS deterioration (p=0·80), or 6-week NIHSS deterioration (p=0·33). The association (predictive testing) between independent variables and primary outcomes in the overall unmatched cohort and subgroups is in the appendix (pp 5, 21–31).

DISCUSSION

We found that awake craniotomy could be a safer and more feasible treatment approach than asleep resection to prevent neurological deficits while pursuing gross total resection for patients with glioblastomas in eloquent areas, and mostly irrespective of age, preoperative NIHSS score, and preoperative KPS. In patients with primary glioblastoma in eloquent areas who were younger than 70 years, with minimal preoperative neurological morbidity (NIHSS 0–1), with a good to excellent preoperative performance score (KPS 90–100), or a combination of these, awake craniotomy seemed to be superior to asleep resection for several primary outcomes and should be considered when assessing the most appropriate surgical strategy. No significant differences were found for NIHSS or KPS deterioration at 6 weeks postoperatively. Survival analyses indicated an overall survival and progression-free survival benefit of awake craniotomy compared with asleep resection in these three subgroups (younger than 70 years, with preoperative NIHSS 0–1, and KPS of 90–100), particularly after 18 months postoperatively. Additionally, our data showed that awake craniotomy was especially beneficial compared with asleep resection for overall survival and progression-free survival in MGMT methylated tumours and that awake craniotomy is strongly associated with the extent of resection. Therefore, we hypothesise that the survival benefit could be caused by the synergistic effect of the greater extent of resection allowed by awake craniotomy than by asleep resection and the heightened sensitivity of MGMT methylated tumours to adjuvant therapy, which corresponds with the visual separation of the Kaplan-Meier curves around 18 months postoperatively.

In the subgroups of patients aged 70 years and older, with a preoperative NIHSS score of 2 or higher, or with a preoperative KPS of 80 or lower, the results were less clear. The number of patients in each of these subgroups who underwent surgery with the use of awake craniotomy over the past 10 years was substantially lower than in the other subgroups, which led to diminished power and precision in analyses. In patients aged 70 years or older or with a preoperative NIHSS score of 2 or higher, awake craniotomy led to less neurological deterioration at 3 months postoperatively, whereas in patients with a preoperative KPS of 80 or lower, it led to less neurological deterioration at 6 months postoperatively. Moreover, awake craniotomy led to a greater extent of resection in all these subgroups and a lower residual volume in the subgroup with a KPS of 80 or lower, irrespective of the patient's preoperative KPS or NIHSS scores. Based on our data, the prevention of these so-called late neurological

complications would be the primary rationale for choosing awake craniotomy in these patient subgroups because the increased extent of resection did not translate into improved overall survival or progression-free survival outcomes. Furthermore, awake craniotomy was predictive of receiving adjuvant chemotherapy and radiotherapy in patients with a preoperative NIHSS score of 2 or higher (appendix pp 26-27). Therefore, optimising clinical performance to enable patients to undergo adjuvant therapy could be an important reason to consider awake craniotomy in these patient subgroups. This hypothesis is supported by our finding that KPS deterioration was strongly predictive of receiving adjuvant therapy and that motor eloquence (NIHSS of ≥2 subgroup) and visual eloquence (KPS ≤80 subgroup) were associated with increased frequency of postoperative NIHSS deterioration in specific subgroups (appendix pp 22-23 and 26-27). However, because high preoperative NIHSS scores can potentially impede the reliability of the testing procedure during awake craniotomy, which could hamper the efficacy and safety of the operation, careful preoperative assessment should be considered vital in patients with an NIHSS score of 2 or higher. In the subgroup of patients with an NIHSS score of 2 or higher, mean residual tumour volume was lower and extent of resection was greater with awake craniotomy than with asleep resection, without affecting survival outcomes, which is similar to the results in the subgroups of patients aged 70 years and older and with a preoperative KPS of 80 or lower. Therefore, our results suggest that awake craniotomy would not be beneficial for improving survival outcomes in these subgroups, although this finding should be interpreted carefully because the number of events in these subgroups was relatively low. This study has several limitations. First, we strived to minimise the risk of confounding and indication biases by using different statistical tools including propensity- score matching, multiple multivariable Cox proportional hazard regressions, and multiple multivariable logistic regressions. Second, we only assessed the residual volume and extent of resection of the contrast-enhancing part of the tumour. Molinaro and colleagues [19] have shown that resection of the non-contrast-enhancing part of the tumour improves overall survival in younger patients (age ≤65 years), regardless of *IDH* or MGMT status. The effect of awake brain mapping on the safety of resecting the non-contrast-enhancing part of the tumour should be an important topic of future research, because preventing neurological deficits by delineating tumour tissue from healthy brain tissue and proper mapping of subcortical functional tracts becomes arguably even more important during such endeavours. However, so-called supratotal resection currently is not considered standard practice by the neurosurgical community. Third, we used the Brodmann classification system to assess tumour eloquence and the NIHSS scale for neurological deficits (which was already the standard assessment method for most study centres). Although these assessments were done in a standardised manner, we cannot fully exclude the possibility of any misclassification or interobserver variability. However, we expect this ratio to be rather low and evenly distributed between and among groups, thereby rendering it unlikely to have significantly affected the results. Fourth, we did not

incorporate the effect of the surgeon experience in the analyses, which might represent a small bias. This is a known problem of non-randomised surgical studies. However, we included study site as a variable in the matching procedure, thereby helping to minimise this effect. Fifth, molecular status (ie, *IDH* mutation and MGMT methylation status) was not available for a small number of patients; however, we successfully included patient age (which is known to be closely related to *IDH* mutation status [20,21]) in the propensity-score matching and molecular status in the Cox proportional hazards regression for optimal minimisation of this effect between groups. Sixth, intraoperative MRI was not used during any of the resections in our cohort. Because intraoperative MRI is not used by most neurosurgeons, the external generalisability of our results should not be affected, although this procedural approach might not necessarily reflect the standard-of-care for a highly selected subgroup of patients treated at specific tertiary centres. Seventh, we did not include preoperative and postoperative neuropsychological testing results of patients because these were not available for a large proportion of our cohort. In most centres, this type of detailed assessment is mostly reserved for patients who undergo awake tumour resection. Instead, we used NIHSS as a measurement scale of postoperative deficits, which is a validated assessment method that has been routinely used in the literature [22,23]. Indeed, postoperative deficits could be divided into level 1 deficits (assessed through routine neurological examination, standardised with the NIHSS—eg, aphasia and paresis) and level 2 deficits (assessed through detailed neuropsychological testing—eg, subtle cognitive impairments). In our randomised, controlled SAFE trial and the prospective PROGRAM cohort study, we included neuropsychological testing as an outcome to address this topic [24–26]. Eighth, we divided the cohort into six subgroups on the basis of variables that are clinically relevant and used to divide patients into distinct subgroups in daily practice. We acknowledge that defining such subgroups using statistical methods, rather than clinically common cutoff values, would be an appropriate research question for future scientific efforts. Ninth, the number of events in the survival analyses could be considered relatively low. Although this is a natural consequence of subgroup analyses, we aimed to minimise this issue by maximising the number of patients in the overall cohort by merging the cohorts of four large institutions, which formed the largest studied cohort of patients with glioblastoma to date, to our knowledge. Tenth, because we assessed the effect of awake craniotomy and various independent factors within various subgroups using a considerable number of analyses, we acknowledge the issue of multiple comparisons and, therefore, care should be taken when interpreting our data. We expect a substantial amount of generalisability of our findings because we used standardised outcome measurements and an inter- national multicentre study design; our findings should be especially generalisable to high-volume university hospitals with a similar study setting, patient selection, and local procedures. Our findings suggest that awake craniotomy would be especially suitable in patients younger than 70 years, with a preoperative NIHSS score of 0–1, or a preoperative KPS of 90–100, in whom

the procedure led to reduced neurological morbidity, an increased amount of tumour resection, and improved overall survival and progression-free survival compared with asleep resection. In patients aged 70 years or older or with a preoperative KPS of 80 or less, awake craniotomy could be useful to prevent late neurological deficits, whereas in patients with a preoperative NIHSS score of 2 or higher it might help them maintain their performance status to undergo adjuvant therapy. The presented findings will be validated in the SAFE trial [24] and the PROGRAM study [26].

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DATA SUPPLEMENT

eMethods 1: Procedures

Tumor resection, awake group

Patients undergoing awake craniotomy are sedated with a bolus injection of propofol (0.5–1 mg/kg) and kept sedated with a propofol infusion pump (mean: 4 mg/kg/h) and remifentanil ((0.5-2 μg/kg/min). Normothermia is maintained with warm-air blankets and warmed infusion lines. The patient is awakened and positioned on the table. At this point local anaesthesia for the fixation of the head in the Mayfield clamp and the surgical field is provided with a mixture of 10 mL lidocaine 2% with 10 mL bupivacaine 0.5% plus adrenaline 1:200,000 for the Mayfield clamp and up to 40 mL bupivacaine 0.375% with adrenaline 1:200,000 for the surgical field. After positioning, clamp fixation, and surgical field infiltration, patients are sedated again for the trephination until the dura mater is opened. Propofol sedation is stopped after opening of the dura, with the patient awakening with as few external stimuli as possible. Cortical stimulation is performed with a bipolar electrical stimulator. The distance between both poles is 5 mm, and stimulation is performed by placing this bipolar forceps directly on the cortical surface and stimulating with increasing electrical biphasic currents of 2–12 mA (1-2 mA increasing steps, pulse frequency 60 Hz, single pulse phase duration of 100 microsec.) until motor or speech arrest is observed. For motor mapping a 2-second train and for speech mapping a 5-second train is used. When localizing language function, the following tests may be used: object naming (Boston naming test or DuLIP (Dutch Linguistic Intraoperative Protocol)), spontaneous speech assessment, counting and calculation, sentence repeat testing. The neurolinguistic expert informs the neurosurgeon of any kind of speech arrest or dysarthria. When localizing the motor and sensory cortex, the patient is asked to report any unintended movement or sensation in extremities or face and perform the finger tapping test. Confirmed functional cortical areas are marked with a number. After completion of cortical mapping, a resection of the tumour is performed as radical as possible using an ultrasonic aspirator (CUSA) and suction tube, while sparing these functional areas. When the tumour margins or white matter is encountered or when the neuronavigation (with or without diffusion tract imaging) indicates proximity of eloquent white matter tracts, subcortical stimulation (biphasic currents of 8–16 mA, 1-2 mA increasing steps, pulse frequency 60 Hz, single pulse phase duration of 100 microsec., 2-second train) is performed to localize functional tracts. If subcortical tracts are identified, resection is stopped in that area. During the resection of the lesion close to an eloquent area, the patient is involved in a continuous dialogue with the neurolinguistic expert. That way the neurosurgeon has 'online'-control of these eloquent areas. In case of beginning disturbances of communication or of motor or sensory sensations the resection is stopped immediately. When, due to stimulation, an epileptic seizure occurs, this is stopped by administering

some drops of iced saline on the just stimulated cortical area. If a seizure continues, an i.v. propofol or diphantoin bolus of 0.5 mg/kg is administrated and repeated until the seizure stops. The mapping procedure is temporarily halted. If the patient is adequate, cooperative, and able to carry out tasks after the seizure, the mapping procedure can continue. In the case of refractory seizures, the mapping procedure will be permanently halted, and the resection will continue under general anesthesia. After resection of the tumor a final neurological examination is performed. During closure of the surgical field the patient is sedated with propofol again. After wound closure and dressing, sedation is stopped. The awake patient is transferred to the post-anaesthesia care unit (PACU), where the patient is hemodynamically and neurologically monitored for 24 hours. The postoperative MRI scan is performed within 72 hours after the operation to assess residual tumor volume and extent of resection. Patients are followed up at the neurosurgical outpatient clinic at 1 week and 6-8 weeks after the operation and with 2–6-month intervals at the neuro-oncological outpatient clinic with neurological examination and MR-imaging. Neurolinguistic follow-up is scheduled at 3 months postoperatively, consisting of DuLIP subset tests, Shortened Token test, Verbal fluency, Comprehensive Aphasia Test, and the Montreal Cognitive Assessment (MOCA).

Tumor resection, asleep group

Patients undergoing asleep tumor resection receive intravenous general anaesthesia with fentanyl 0.25-0.5 mg, propofol 100-200 mg and cisatracurium 10-20 mg. After induction of anaesthesia, patient is orotracheally intubated and mechanical ventilation is applied. Respiratory rate and tidal volume are adjusted to keep the patient normocapnic. Anaesthesia is maintained with propofol (up to 10 mg/kg/h) and remifentanil (0.5-2 μg/kg/min). isoflurane (up to 1 MAC) and clonidine (1-2 μg/kg) may be added for maintenance, if necessary (a beta blocker or calcium channel blocker may be used to control BP as an alternative to clonidine). 0.9% saline solution and balanced crystalloids are used for maintenance, in case of blood loss > 300 ml, HAES 130/0.4 solution will be given. Normothermia is maintained with warm-air blankets and warmed infusion lines. Local infiltration of the scalp is performed with 20 ml lidocaine 1% with adrenaline 1:200.000 to reduce bleeding. The insertion points of the Mayfield clamp are not infiltrated with local anaesthetics. Trephination and tumour resection are performed without any additional neuro-psychological monitoring, guided by standard neuronavigation. At the end of the procedure all anaesthetics are stopped and the patient is brought to the post-anesthesia care unit (PACU). Detubation of the patient is performed as early as possible, if patient fulfils the detubation criteria (>36 C body temperature, stable hemodynamics, sufficient spontaneous ventilation, adequate response to verbal orders). At the PACU, the patient is hemodynamically and neurologically monitored for 24 hours. Patients who have undergone asleep resection receive the same standard follow up as the patients who have undergone awake craniotomy.

eResults 1: Participating sites

Erasmus Medical Center, Rotterdam, The Netherlands
Principal Investigator: dr. A.J.P.E. Vincent
Number of included patients: 382

Haaglanden Medical Center, The Hague, The Netherlands
Principal Investigator: dr. M.L.D. Broekman
Number of included patients: 354

Brigham and Women's Hospital, Boston MA, USA
Principal Investigator: dr. T.R. Smith
Number of included patients: 200

University Hospital Leuven, Belgium
Principal Investigator: prof. dr. S. De Vleeschouwer
Number of included patients: 111

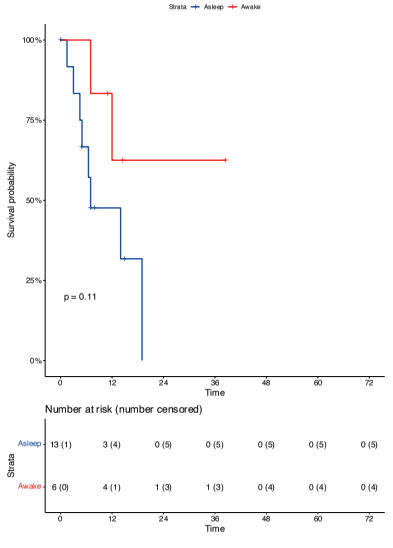
eResults 2: Predictive testing: Association of other perioperative factors with primary outcomes

The association of awake mapping and other perioperative factors with primary outcomes was assessed using predictive testing with multiple multivariable logistic regression analyses. Predictive testing using multiple multivariable logistic regression analyses for the overall cohort indicated that Overall, 6-week KPS deterioration was associated with an increased risk of 6-week NIHSS deterioration (OR 7.62 [5.13-11.3], p <0.001) as well as visual eloquence of the tumor (OR 1.78 [1.07-2.95], p = 0.026) (pages 16-17, Data Supplement). The risk of 6-week KPS deterioration was increased by a higher age (OR 1.03 [1.01-1.05], p<0.001) and 6-week NIHSS deterioration (OR 7.46 [5.02-11.1], p<0.001) (pages 18-19, Data Supplement). Younger patients (OR 0.95 [0.92-0.98], p = 0.001) received significantly more often adjuvant chemotherapy and radiotherapy, while patients with 6-week KPS deterioration received less often adjuvant therapy (OR 0.18 [0.10-0.34], p = 0.001) (pages 20-21, Data Supplement). Overall, intraoperative ultrasound was significantly predictive for gross-total resection based on residual tumor volume (OR 1.68 [1.04-2.72], p = 0.034) and extent of resection (OR 1.62 [1.03-2.54], p = 0.036) (pages 22-25, Data Supplement). Furthermore, occipital location of the tumor (OR 5.41 [1.10-26.7], p = 0.038) was predictive for gross-total resection based on residual tumor volume. Regression analyses for insular tumors were not possible due to inappropriate number of available cases in our cohort.

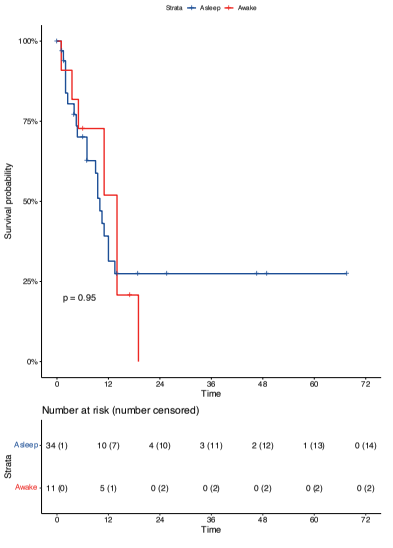
The predictive value of various factors was for most subgroups in line with the results for the overall cohort with some notable nuances (pages 16-25, Data Supplement). There was a clear co-occurrence of postoperative KPS deterioration and NIHSS deterioration. In younger patients, motor-eloquent, language-eloquent or visual-eloquent tumors were significantly predictive of postoperative NIHSS deterioration (motor: OR 3.98 [1.63-9.70], p = 0.002; language: OR 5.30 [1.92-14.6], p = 0.001; visual: OR 2.65 [1.15-6.09], p = 0.022). For motor-eloquent tumors this was also the case in the NIHSS ≥ 2 subgroup (OR 2.89 [1.68-49.7], p = 0.018) and for visual-eloquent tumors in the KPS ≤ 80 subgroup (OR 13.8 [1.20-160], p = 0.033). Higher age was negatively predictive for receival of adjuvant chemotherapy and radiotherapy in the subgroups NIHSS 0-1 (OR 0.95 [0.91-0.98], p = 0.004), NIHSS ≥ 2 (OR 0.93 [0.87-0.98], p = 0.011) and KPS ≤ 80 (OR 0.95 [0.92-0.99], p = 0.015). KPS deterioration was found to be strongly predictive as well of receiving adjuvant therapy, except for the KPS 90-100 subgroup (OR 0.39 [0.13-1.20], p = 0.10). Moreover, motor-eloquent location of the tumor was negatively predictive for gross-total resection based on residual tumor volume in the ≥ 70 years subgroup (OR 0.04 [0.00-0.70], p = 0.20) and the NIHSS ≥ 2 subgroup (OR 0.07 [0.01-0.44], p = 0.004), and language-eloquent location in the NIHSS ≥ 2 subgroup as well (OR 0.08 [0.01-0.58], p = 0.012).

eResults 3: Kaplan-Meier curves for Overall Survival for subgroups based on age, stratified by MGMT methylation status

H Matched subgroups ≥ 70 years – MGMT methylated

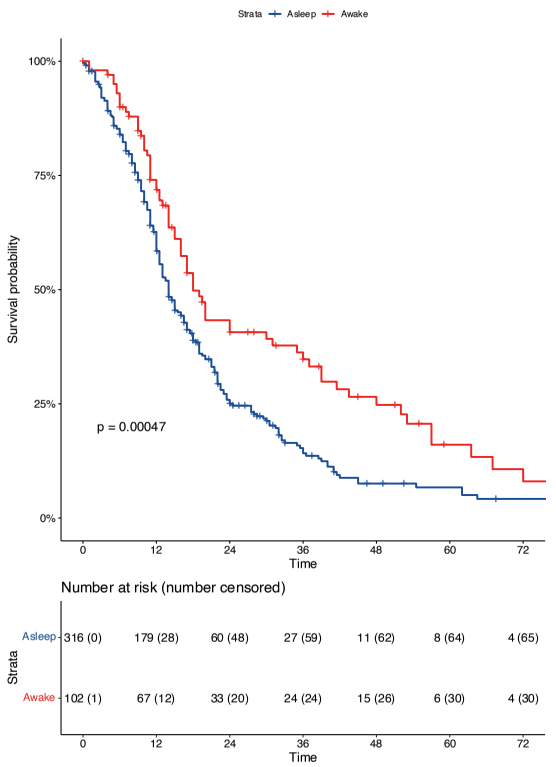


I Matched subgroups ≥ 70 years – MGMT unmethylated

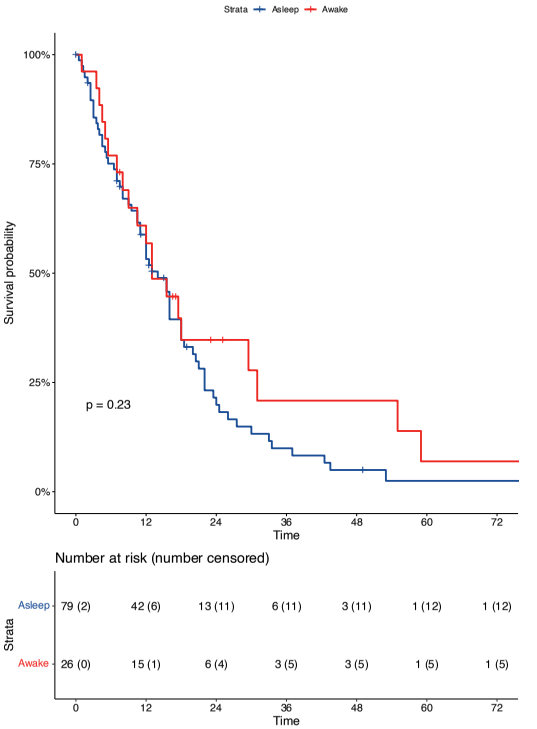


eResults 4: Kaplan-Meier curves for Overall Survival for subgroups based on preoperative NIHSS score

J Matched subgroups NIHSS 0-1

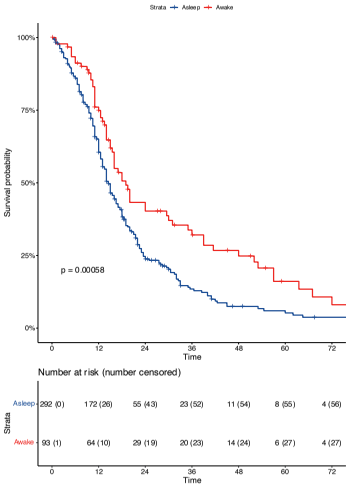


K Matched subgroups NIHSS ≥ 2

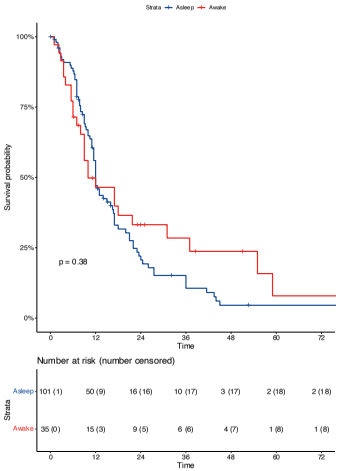


eResults 5: Kaplan-Meier curves for Overall Survival for subgroups based on preoperative KPS

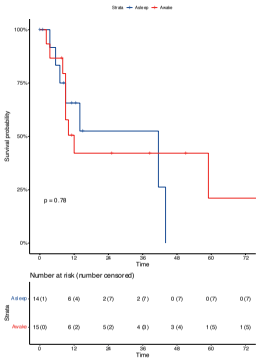
L Matched subgroups KPS 90-100



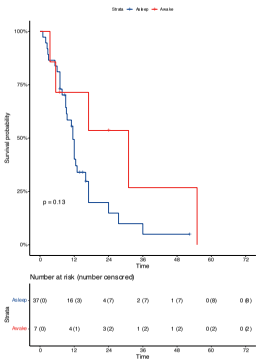
M Matched subgroups KPS ≤ 80



N Matched subgroups KPS ≤ 80 – MGMT methylated



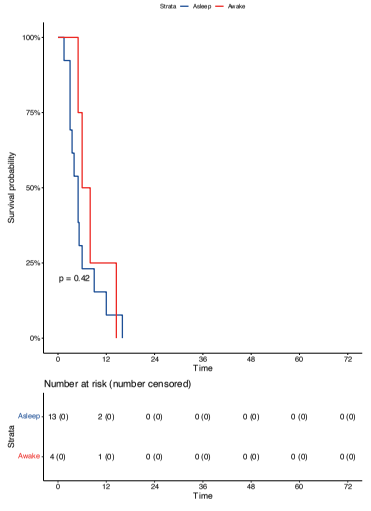
O Matched subgroups KPS ≤ 80 – MGMT unmethylated



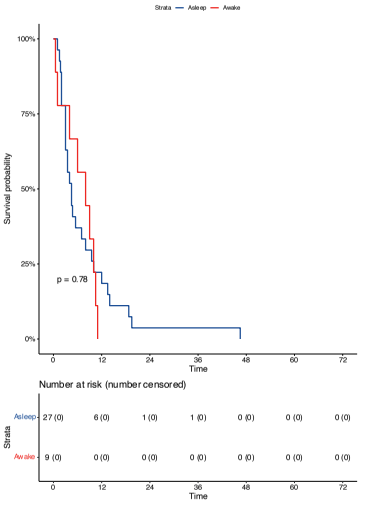
Data are shown for those aged ≥70 years stratified by MGMT methylation status (H, I), for the matched subgroups based on preoperative NIHSS score (J, K), for the matched subgroups based on preoperative KPS (L, M) and for those with a preoperative KPS of ≤80 stratified by MGMT methylation status (N, O). H: median OS for the awake group (n=6, 2 events) was NA (95% CI 12.0-NA) versus 7.0 months (95% CI 5.0-NA) for the asleep group (n=15, 8 events). I: median OS for the awake group (n=11, 9 events) was 14.0 months (95% CI 11.0-NA) versus 10.0 months (95% CI 7.0-NA) for the asleep group (n=34, 20 events). J: median OS for the awake group (n=107, 70 events) was 18.0 months (95% CI 16.0-31.0) versus 14.0 months (95% CI 13.0-16.5) for the asleep group (n=321, 248 events). K: median OS for the awake group (n=27, 20 events) was 10.0 months (95% CI 5.0-24.0) versus 8.5 months (95% CI 5.0-18.0) for the asleep group (n=81, 66 events). L: median OS for the awake group (n=99, 64 events) was 19.0 months (95% CI 16.0-31.0) versus 14.5 months (95% CI 13.0-16.5) for the asleep group (n=297, 233 events). M: median OS for the awake group (n=35, 26 events) was 10.0 months (95% CI 9.0-37.0) versus 12.0 months (95% CI 11.5-16.8) for the asleep group (n=135, 81 events). N: median OS for the awake group (n=15, 9 events) was 41.5 months (95% CI 9.0-NA) versus 12.0 months (95% CI 9.0-NA) for the asleep group (n=14, 7 events). O: median OS for the awake group (n=7, 5 events) was 31.0 months (95% CI 5.5-NA) versus 11.5 months (95% CI 9.25-17.0) for the asleep group (n=37, 29 events). Groups are described on pages 14-21 of the Data Supplement. KPS = Karnofsky Performance Score. NIHSS = National Institute of Health Stroke Scale. MGMT = promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase

eResults 6: Kaplan-Meier curves for Progression-Free Survival for subgroups based on age, stratified by MGMT methylation status

H Matched subgroups ≥ 70 years – MGMT methylated

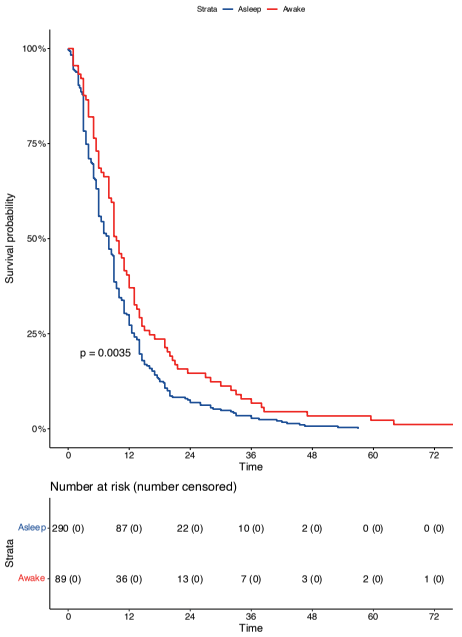


I Matched subgroups ≥ 70 years – MGMT unmethylated

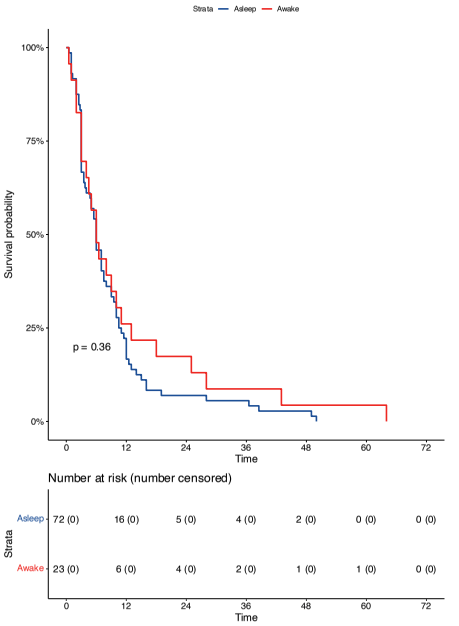


eResults 7: Kaplan-Meier curves for Progression-Free Survival for subgroups based on preoperative NIHSS score

J Matched subgroups NIHSS 0-1

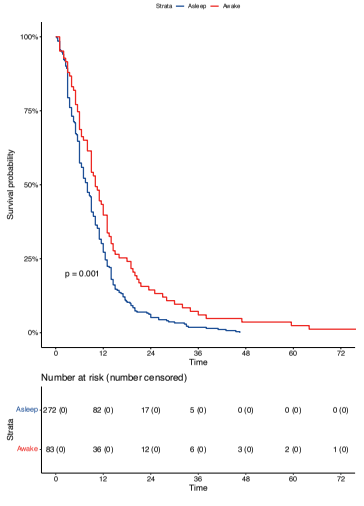


K Matched subgroups NIHSS ≥ 2

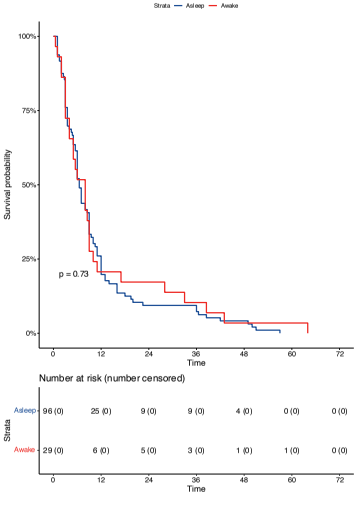


eResults 8: Kaplan-Meier curves for Progression-Free Survival based on preoperative KPS

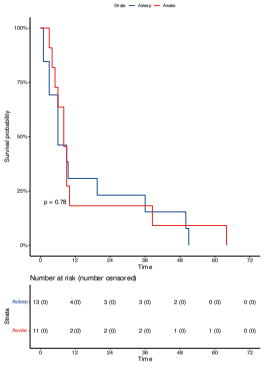
L Matched subgroups KPS 90-100



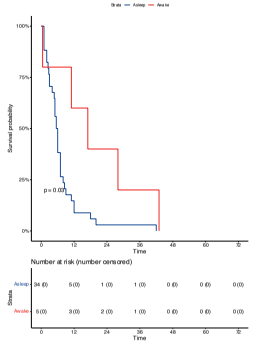
M Matched subgroups KPS ≤80



N Matched subgroups KPS ≤ 80 – MGMT methylated



O Matched subgroups KPS ≤80 – MGMT unmethylated



Data are shown for those aged ≥70 years stratified by MGMT methylation status (H, I), for the matched subgroups based on preoperative NIHSS score (J, K), for the matched subgroups based on preoperative KPS (L, M) and for those with a preoperative KPS of ≤80 stratified by MGMT methylation status (N, O). H: median PFS for the awake group (n=4, 4 events) was 7.0 months (95% CI 5.0-NA) versus 5.0 months (95% CI 3.0-NA) for the asleep group (n=13, 13 events). I: median PFS for the awake group (n=9, 9 events) was 8.0 months (95% CI 4.0-NA) versus 4.5 months (95% CI 3.0-9.5) for the asleep group (n=27, 27 events). J: median PFS for the awake group (n=89, 89 events) was 9.5 months (95% CI 9.0-12.0) versus 8.0 months (95% CI 6.5-9.0) for the asleep group (n=290, 290 events). K: median PFS for the awake group (n=23, 23 events) was 10.0 months (95% CI 9.0-13.0) versus 8.0 months (95% CI 7.0-9.0) for the asleep group (n=72, 72 events). L: median PFS for the awake group (n=83, 83 events) was 10.0 months (95% CI 9.0-13.0) versus 8.0 months (95% CI 7.0-9.0) for the asleep group (n=272, 272 events). M: median PFS for the awake group (n=29, 29 events) was 8.0 months (95% CI 5.0-9.0) versus 6.5 months (95% CI 6.0-9.0) for the asleep group (n=96, 96 events). N: median PFS for the awake group (n=11, 11 events) was 8.0 months (95% CI 6.0-NA) versus 6.0 months (95% CI 3.0-NA) for the asleep group (n=13, 13 events). O: median PFS for the awake group (n=5, 5 events) was 17.0 months (95% CI 11.0-NA) versus 5.8 months (95% CI 5.0-7.0) for the asleep group (n=34, 34 events). Groups are described on pages 14-21 of the Data Supplement. KPS = Karnofsky Performance Score. NIHSS = National Institute of Health Stroke Scale. MGMT = promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase

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eTable 1: Summary data for glioblastoma subgroups based on age

Characteristic	<70 years old, matched (1:3)			≥ 70 years old, matched (1:3)		
	Awake craniotomy (n = 114)	**Asleep resection (n = 342)**	***p* value**	**Awake craniotomy (n = 20)**	**Asleep resection (n = 60)**	***p* value**
Center			<0.0001			0.13
Rotterdam	42/114 (36.8)	159/342 (46.5)		2/20 (10.0)	9/60 (15.0)	
The Hague	18/114 (15.8)	115/342 (33.6)		6/20 (30.0)	41/60 (68.3)	
Leuven	24/114 (21.1)	55/342 (16.1)		3/20 (15.0)	14/60 (23.3)	
Boston	30/114 (26.3)	13/342 (3.8)		9/20 (45.0)	16/60 (26.7)	
Year of surgery			0.10			0.52
2010-2015	28/114 (24.6)	114/342 (19.0)		5/20 (25.0)	11/60 (18.3)	
2016-2020	86/114 (75.4)	277/342 (81.0)		15/20 (75.0)	49/60 (81.7)	
Gender			0.82			1.000
Male	78/114 (68.4)	228/342 (66.7)		12/20 (60.0)	35/60 (58.3)	
Female	36/114 (31.6)	114/342 (33.3)		8/20 (40.0)	25/60 (41.7)	
Age at diagnosis, years			0.39			0.47
Mean (SD)	54.4 (11.0)	57.1 (9.1)		75.3 (0.5)	75.5 (3.9)	
Median (IQR)	55.5 (48.3-63.4)	58.0 (52.0-65.0)		73.5 (70.0-78.3)	75.0 (72.0-79.0)	
Range	22.0-69.0	20.0-69.0		70.0-87.0	70.0-86.0	
Preoperative KPS			0.52			0.82
<60	1/114 (0.9)	0/342 (0.0)		0/20 (0.0)	0/60 (0.0)	
60	1/114 (0.9)	9/342 (2.6)		0/20 (0.0)	0/60 (0.0)	
70	6/114 (5.3)	31/342 (9.1)		0/20 (0.0)	3/60 (5.0)	
80	20/114 (17.5)	98/342 (28.7)		7/20 (35.0)	14/60 (23.3)	
90	56/114 (49.1)	154/342 (45.0)		9/20 (45.0)	27/60 (45.0)	
100	30/114 (26.3)	50/342 (14.6)		4/20 (20.0)	16/60 (26.7)	
Median preoperative KPS (IQR)	90 (90-100)	90 (80-90)		90 (80-90)	90 (80-100)	

eTable 1: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:3)			≥ 70 years old, matched (1:3)		
	Awake craniotomy (n = 114)	Asleep resection (n = 342)	*p* value	Awake craniotomy (n = 20)	Asleep resection (n = 60)	*p* value
Preoperative ASA score			0.064			0.64
I	17/114 (14.9)	61/342 (17.8)		0/17 (0.0)	4/60 (6.7)	
II	56/114 (49.1)	222/342 (64.9)		7/17 (41.2)	30/60 (50.0)	
III	29/114 (25.4)	56/342 (16.4)		10/17 (58.8)	25/60 (41.7)	
IV	0/114 (0.0)	3/342 (0.9)		0/17 (0.0)	1/60 (1.7)	
Median preoperative ASA score (IQR)	1 (0-1)	1 (0-1)		2 (2-3)	2 (2-3)	
Preoperative NIHSS score			0.066			0.72
0	58/114 (50.9)	133/342 (38.9)		5/20 (25.0)	21/60 (35.0)	
1	34/114 (29.8)	104/342 (30.4)		10/20 (50.0)	18/60 (30.0)	
2	13/114 (11.4)	58/342 (17.0)		4/20 (20.0)	12/60 (20.0)	
3	2/114 (1.8)	24/342 (7.0)		1/20 (5.0)	4/60 (6.7)	
4	4/114 (3.5)	10/342 (2.9)		0/20 (0.0)	2/60 (3.3)	
>4	3/114 (2.6)	13/342 (3.8)		0/20 (0.0)	3/60 (5.0)	
Median preoperative NIHSS score (IQR)	0 (0-1)	0 (0-2)		1 (1-1)	0 (0-1)	
Tumor location by lobe			0.042			0.36
Frontal	45/114 (39.5)	114/342 (33.3)		6/20 (30.0)	17/60 (28.3)	
Parietal	30/114 (26.3)	80/342 (23.4)		3/20 (15.0)	18/60 (30.0)	
Temporal	36/114 (31.6)	126/342 (36.8)		11/20 (55.0)	18/60 (30.0)	
Occipital	1/114 (0.9)	22/342 (6.4)		0/20 (0.0)	5/60 (8.3)	
Insula	2/114 (1.8)	0/342 (0.0)		0/20 (0.0)	1/60 (1.7)	
Tumor location by hemisphere			0.013			0.89
Left	94/114 (82.5)	240/342 (70.2)		14/20 (70.0)	41/60 (68.3)	
Right	20/114 (17.5)	102/342 (29.8)		6/20 (30.0)	19/60 (31.7)	
Tumor location by eloquence			0.0045			0.18
Motor	53/114 (46.5)	154/342 (45.0)		8/20 (40.0)	28/60 (46.7)	
Sensory	4/114 (3.5)	16/342 (4.7)		0/20 (0.0)	5/60 (8.3)	
Language	62/114 (54.4)	148/342 (43.4)		14/20 (70.0)	27/60 (45.0)	
Visual	16/114 (14.0)	111/3432 (32.5)		0/20 (0.0)	14/60 (23.3)	

eTable 1: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:3)			≥ 70 years old, matched (1:3)		
	Awake craniotomy (n = 114)	**Asleep resection (n = 342)**	***p* value**	**Awake craniotomy (n = 20)**	**Asleep resection (n = 60)**	***p* value**
IDH status			0.49			0.57
Wildtype	83/94 (88.3)	187/214 (87.4)		18/18 (100.0)	48/52 (92.3)	
Mutant	11/94 (11.7)	27/214 (12.6)		0/18 (0.0)	4/52 (7.7)	
MGMT status			0.0011			0.72
Methylated	36/72 (50.0)	55/192 (28.5)		6/17 (64.7)	15/49 (30.6)	
Unmethylated	36/72 (50.0)	137/192 (71.0)		11/17 (35.3)	34/49 (69.4)	
Surgical adjuncts						
Intraoperative ultrasound	21/114 (18.4)	38/342 (11.1)	0.064	7/20 (35.0)	5/60 (8.3)	0.0038
Intraoperative fluorescence	26/114 (22.8)	68/342 (19.9)	0.59	3/20 (15.0)	11/60 (18.3)	0.73
Postoperative adjuvant therapy			0.039			0.68
Radiotherapy only	1/114 (0.9)	21/342 (6.1)		2/20 (10.0)	7/60 (11.7)	
Chemotherapy only	3/114 (2.6)	4/342 (1.2)		0/20 (0.0)	0/60 (0.0)	
Chemoradiotherapy	105/114 (92.1)	289/342 (84.5)		17/20 (85.0)	45/60 (75.0)	
None	5/114 (4.4)	28/342 (8.2)		1/20 (5.0)	7/60 (11.7)	
Reasons for no combined CTx + RTx			0.43			0.75
Due to surgical deficits	1/9 (11.1)	12/53 (22.6)		0/3 (0.0)	1/14 (7.1)	
Due to rapid progression	2/9 (22.2)	6/53 (11.3)		0/3 (0.0)	1/14 (7.1)	
Pre-op already ineligible	3/9 (33.3)	26/53 (49.1)		3/3 (100.0)	11/14 (78.6)	
Patient's wish	1/91 (11.1)	6/53 (11.3)		0/3 (0.0)	1/14 (7.1)	
Due to inclusion in clinical trial	1/9 (11.1)	1/53 (1.9)		0/3 (0.0)	0/14 (0.0)	
Unknown	1/9 (11.1)	2/53 (3.8)		0/3 (0.0)	0/14 (0.0)	

eTable 1: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:3)			≥ 70 years old, matched (1:3)		
	Awake craniotomy (n = 114)	Asleep resection (n = 342)	*p* value	Awake craniotomy (n = 20)	Asleep resection (n = 60)	*p* value
6-week NIHSS-status, pre-op as ref						
Deteriorated	23/109 (21.1)	84/327 (25.7)	0.34	3/20 (15.0)	13/55 (23.6)	0.42
New	12/23 (52.2)	36/84 (42.9)		0/3 (0.0)	7/12 (58.3)	
Worsened	11/23 (47.8)	48/84 (57.1)		3/3 (100.0)	5/12 (41.7)	
Transient	5/23 (21.7)	7/84 (8.3)		0/3 (0.0)	1/12 (8.3)	
Permanent	18/23 (78.3)	77/84 (91.7)		3/3 (100.0)	11/12 (91.7)	
Improved	28/109 (25.7)	69/327 (25.4)	0.32	5/20 (25.0)	12/55 (21.8)	0.77
Stable	58/109 (53.2)	150/327 (45.9)	0.090	12/20 (60.0)	30/55 (54.5)	0.67
6-week KPS status, pre-op as ref						
Deteriorated	34/110 (30.9)	118/331 (35.6)	0.36	11/18 (61.1)	31/57 (54.4)	0.62
Improved	23/110 (20.9)	75/331 (22.7)	0.70	4/18 (22.2)	6/57 (10.5)	0.20
Stable	53/110 (48.2)	138/331 (41.7)	0.23	3/18 (16.7)	20/57 (35.1)	0.14
3-month NIHSS-status, pre-op as ref						
Deteriorated	22/103 (21.4)	93/272 (34.2)	0.016	2/16 (12.5)	15/35 (42.9)	0.033
New	12/103 (54.5)	43/93 (46.2)		0/2 (0.0)	6/15 (40.0)	
Worsened	10/22 (45.5)	50/93 (53.8)		3/2 (100.0)	9/15 (60.0)	
Improved	28/103 (27.2)	69/272 (25.4)	0.72	5/16 (31.3)	7/35 (20.0)	0.38
Stable	53/103 (51.5)	110/272 (40.4)	0.055	9/16 (56.3)	15/35 (42.9)	0.63
3-month KPS status, pre-op as ref						
Deteriorated	38/103 (36.9)	113/277 (49.8)	0.49	2/16 (12.5)	3/35 (8.6)	0.66
Improved	19/103 (18.4)	63/277 (22.7)	0.37	8/16 (50.0)	20/35 (57.1)	0.63
Stable	46/103 (44.7)	101/277 (36.5)	0.14	6/16 (37.5)	12/35 (34.3)	0.82
6-month NIHSS-status, pre-op as ref						
Deteriorated	24/101 (23.8)	108/258 (41.9)	0.0014	4/14 (28.6)	13/33 (39.4)	0.48
New	15/24 (62.5)	54/108 (50.0)		0/4 (0.0)	6/13 (46.2)	
Worsened	9/24 (37.5)	54/108 (50.0)		4/4 (100.0)	7/13 (53.8)	
Improved	29/101 (28.7)	63/258 (24.2)	0.40	4/14 (28.6)	4/33 (12.1)	0.17
Stable	48/101 (47.5)	87/258 (33.7)	0.0080	6/14 (42.9)	16/33 (48.5)	0.72

eTable 1: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:3)			≥ 70 years old, matched (1:3)		
	Awake craniotomy (n = 114)	**Asleep resection (n = 342)**	***p* value**	**Awake craniotomy (n = 20)**	**Asleep resection (n = 60)**	***p* value**
6-month KPS status, pre-op as ref						
Deteriorated	42/102 (41.2)	124/259 (47.9)	0.25	9/15 (60.0)	3/33 (9.1)	<0.0001
Improved	19/102 (18.6)	52/259 (20.1)	0.76	0/15 (0.0)	21/33 (63.6)	<0.0001
Stable	41/102 (40.2)	83/259 (32.0)	0.015	6/15 (40.0)	9/33 (27.3)	0.38
Postoperative vascular complications			0.39			0.55
None	109/112 (97.3)	315/335 (95.0)		20/20 (100.0)	59/60 (98.3)	
Major ischemia	2/112 (1.8)	14/335 (4.2)		0/20 (0.0)	1/60 (1.7)	
Postoperative (reactive) bleeding	1/112 (0.9)	6/335 (1.8)		0/20 (0.0)	0/60 (0.0)	
Preoperative CE tumor volume, ml			0.087			0.56
Mean (SD)	39.4 (48.0)	52.6 (40.5)		31.3 (40.2)	38.6 (32.4)	
Median (Q1-Q3)	24.2 (12.2-51.0)	41.1 (23.3-71.1)		17.3 (9.0-34.2)	26.4 (16.7-55.9)	
Range	0.8-208.0	1.6-212.0		2.7-160.1	0.8-139.8	
Postoperative CE tumor volume, ml			<0.0001			0.11
Mean (SD)	2.1 (6.0)	6.6 (12.3)		0.4 (7.6)	2.4 (5.9)	
Median (Q1-Q3)	0.8 (0.0-1.4)	1.8 (0.8-6.6)		0.0 (0.0-0.3)	0.7 (0.0-1.5)	
Range	0.0-41.0	0.0-81.7		0.0-2.4	0.0-36.0	
Extent of resection CE tumor, % by volume			<0.0001			0.036
Mean (SD)	95.7 (8.1)	86.3 (19.6)		98.2 (3.6)	90.5 (17.3)	
Median (Q1-Q3)	99.8 (95.4-100.0)	95.3 (81.1-99.6)		100.0 (98.8-100.0)	96.7 (88.7-100.0)	
Range	48.2-100.0	21.0-100.0		87.5-100.0	39.5-100.0	
Median progression-free survival, months (95% CI)	9.3 (8.0-12.0)	7.5 (6.5-9.0)	0.0061	8.0 (5.0-11.0)	5.3 (4.0-9.5)	0.99
Median overall survival, months (95% CI)	19.5 (16.0-31.0)	15.0 (13.0-17.0)	<0.0001	12.0 (11.0-NA)	10.5 (9.0-16.0)	0.66

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the matched age cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

eTable 2: Summary data for glioblastoma subgroups based on preoperative NIHSS score

Characteristic	NIHSS score 0-1, matched (1:3)			NIHSS score ≥ 2, matched (1:3)		
	Awake craniotomy (n = 107)	**Asleep resection (n = 321)**	***p* value**	**Awake craniotomy (n = 27)**	**Asleep resection (n = 81)**	***p* value**
Center			<0.0001			0.342
Rotterdam	36/107 (33.6)	154/321 (48.0)		8/27 (29.6)	34/81 (42.0)	
The Hague	18/107 (16.8)	126/321 (39.3)		6/27 (22.2)	17/81 (21.0)	
Leuven	19/107 (17.8)	30/321 (9.35)		8/27 (29.6)	24/81 (29.6)	
Boston	34/107 (31.8)	11/321 (3.43)		6/27 (18.5)	6/81 (7.4)	
Year of surgery			0.57			0.10
2010-2015	38/107 (35.6)	106/321 (33.0)		10/27 (37.0)	40/81 (49.4)	
2016-2020	73/107 (68.2)	232/321 (67.0)		21/27 (63.0)	41/81 (51.6)	
Gender			0.813			0.502
Male	73/107 (68.2)	213/321 (66.4)		17/27 (63.0)	43/81 (53.1)	
Female	34/107 (31.8)	108/321 (33.6)		10/27 (37.0)	38/81 (46.9)	
Age at diagnosis, years			0.25			0.86
Mean (SD)	58.4 (12.8)	60.5 (11.0)		62.0 (11.6)	62.7 (11.6)	
Median (IQR)	58.0 (49.0-66.0)	61.0 (53.0-69.0)		65.0 (56.0-69.0)	65.0 (55.0-70.0)	
Range	22.0-87.0	23.0-86.0		34.0-82.0	20.0-83.0	
Preoperative KPS			0.10			0.94
<60	0/107 (0.0)	0/321 (0.0)		1/27 (3.7)	1/81 (1.2)	
60	1/107 (0.9)	0/321 (0.0)		0/27 (0.0)	3/81 (3.7)	
70	3/107 (2.8)	18/321 (5.6)		3/27 (11.1)	8/81 (9.9)	
80	15/107 (14.0)	66/321 (20.6)		12/27 (44.4)	39/81 (48.1)	
90	55/107 (51.4)	172/321 (53.6)		10/27 (37.0)	28/81 (34.6)	
100	33/107 (30.8)	65/321 (20.2)		1/27 (3.7)	2/81 (2.5)	
Median preoperative KPS (IQR)	90 (80-90)	90 (80-90)		80 (80-90)	80 (80-90)	

eTable 2: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:3)			NIHSS score ≥ 2, matched (1:3)		
	Awake craniotomy (n = 107)	Asleep resection (n = 321)	*p* value	Awake craniotomy (n = 27)	Asleep resection (n = 81)	*p* value
Preoperative ASA score			0.0074			0.66
I	14/107 (13.1)	52/321 (16.2)		3/27 (11.1)	7/81 (8.6)	
II	50/107 (46.7)	212/321 (66.0)		13/27 (48.1)	53/81 (65.4)	
III	32/107 (29.9)	56/321 (17.4)		7/27 (25.9)	21/81 (25.9)	
IV	0/107 (0.0)	1/321 (0.3)		0/27 (0.0)	0/81 (0.0)	
Median preoperative ASA score (IQR)	2 (2-2)	2 (2-2)		2 (2-3)	2 (2-3)	
Preoperative NIHSS score			0.43			0.18
0	63/107 (58.9)	175/321 (54.5)		0/27 (0.0)	0/81 (0.0)	
1	44/107 (41.1)	146/321 (45.5)		0/27 (0.0)	0/81 (0.0)	
2	0/107 (0.0)	0/321 (0.0)		17/27 (63.0)	50/81 (61.7)	
3	0/107 (0.0)	0/321 (0.0)		3/27 (11.1)	15/81 (18.5)	
4	0/107 (0.0)	0/321 (0.0)		4/27 (14.8)	3/81 (3.7)	
>4	0/107 (0.0)	0/321 (0.0)		3/27 (11.1)	13/81 (16.0)	
Median preoperative NIHSS score (IQR)	0 (0-1)	0 (0-1)		2 (2-4)	2 (2-3)	
Tumor location by lobe			0.16			0.45
Frontal	40/107 (37.4)	101/321 (31.5)		11/27 (40.7)	30/81 (37.0)	
Parietal	26/107 (24.3)	76/321 (23.7)		7/27 (25.9)	18/81 (22.2)	
Temporal	40/107 (37.4)	125/321 (38.9)		7/27 (25.9)	19/81 (23.5)	
Occipital	1/107 (0.9)	19/321 (5.9)		0/27 (0.0)	13/81 (16.0)	
Insula	0/197 (0.0)	0/321 (0.0)		2/27 (7.4)	0/81 (0.0)	
Tumor location by hemisphere			0.057			0.554
Left	84/107 (78.5)	219/321 (68.2)		24/27 (88.9)	67/81 (82.7)	
Right	23/107 (21.5)	102/321 (31.8)		3/27 (11.1)	14/81 (17.3)	
Tumor location by eloquence			0.023			0.0060
Motor	48/107 (44.9)	147/321 (45.8)		13/27 (48.1)	46/81 (56.8)	
Sensory	2/107 (1.9)	9/321 (2.8)		2/27 (7.4)	4/81 (4.9)	
Language	60/107 (56.1)	150/321 (46.7)		16/27 (59.3)	21/81 (25.9)	
Visual	11/107 (10.3)	79/321 (24.6)		5/27 (18.5)	42/81 (51.9)	

eTable 2: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:3)			NIHSS score ≥ 2, matched (1:3)		
	Awake craniotomy (n = 107)	Asleep resection (n = 321)	*p* value	Awake craniotomy (n = 27)	Asleep resection (n = 81)	*p* value
IDH status			0.410			0.565
Wildtype	82/93 (88.2)	183/199 (92.0)		19/19 (100.0)	52/55 (94.5)	
Mutant	11/92 (11.8)	16/199 (8.0)		0/19 (0.0)	3/55 (94.5)	
MGMT status			0.169			0.088
Methylated	31/71 (43.7)	71/221 (33.6)		11/18 (61.1)	14/38 (36.8)	
Unmethylated	40/71 (56.3)	140/221 (66.4)		7/18 (38.9)	24/38 (63.2)	
Surgical adjuncts						
Intraoperative ultrasound	24/107 (22.4)	32/221 (10.0)	0.073	4/27 (14.8)	11/81 (13.6)	0.87
Intraoperative fluorescence	21/107 (19.6)	38/221 (11.8)	0.063	8/27 (29.6)	26/81 (32.1)	0.81
Postoperative adjuvant therapy			0.014			0.47
Radiotherapy only	3/107 (2.8)	25/321 (7.8)		0/27 (0.0)	10/81 (12.3)	
Chemotherapy only	3/107 (2.8)	1/321 (0.31)		0/27 (0.0)	1/81 (1.2)	
Chemoradiotherapy	98/107 (91.6)	320/321 (99.7)		24/27 (88.9)	62/81 (77.8)	
None	3/107 (2.8)	23/321 (7.2)		3/27 (11.1)	6/81 (7.4)	
Reasons for no combined CTx + RTx			0.71			0.46
Due to surgical deficits	0/9 (0.0)	13/49 (26.5)		1/3 (33.3)	2/19 (22.2)	
Due to rapid progression	2/9 (22.2)	6/49 (12.2)		0/3 (0.0)	1/19 (5.3)	
Pre-op already ineligible	5/9 (55.5)	20/49 (40.8)		1/3 (33.3)	10/19 (52.6)	
Patient's wish	1/9 (11.1)	7/49 (14.3)		0/3 (0.0)	1/19 (5.3)	
Due to inclusion in clinical trial	1/9 (11.1)	2/49 (4.1)		0/3 (0.0)	0/19 (0.0)	
Unknown	0/9 (11.1)	1/49 (2.0)		1/3 (33.3)	5/19 (26.3)	

eTable 2: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:3)			NIHSS score ≥ 2, matched (1:3)		
	Awake craniotomy (n = 107)	Asleep resection (n = 321)	*p* value	Awake craniotomy (n = 27)	Asleep resection (n = 81)	*p* value
6-week NIHSS-status, pre-op as ref						
Deteriorated	22/100 (22.0)	93/307 (30.3)	0.11	5/27 (18.5)	16/81 (19.8)	0.91
New	12/22 (54.5)	53/93 (57.0)		0/5 (0.0)	0/16 (0.0)	
Worsened	10/22 (45.5)	40/93 (43.0)		5/5 (100.0)	16/16 (100.0)	
Transient	4/22 (18.2)	7/53 (13.4)		2/5 (40.0)	0/16 (0.0)	
Permanent	18/22 (81.8)	46/53 (86.8)		3/5 (60.0)	16/16 (100.0)	
Improved	17/100 (17.0)	56/307 (18.2)	0.78	15/27 (55.6)	37/81 (45.7)	0.37
Stable	61/100 (61.0)	158/307 (51.5)	0.10	7/27 (25.9)	28/81 (34.6)	0.41
6-week KPS status, pre-op as ref						
Deteriorated	35/102 (34.3)	126/310 (40.6)	0.26	11/26 (42.3)	36/80 (45.0)	0.81
Improved	21/102 (20.6)	55/310 (17.7)	0.52	6/26 (23.1)	21/80 (26.3)	0.75
Stable	46/102 (45.1)	129/310 (41.6)	0.54	9/27 (33.3)	23/80 (28.8)	0.65
3-month NIHSS-status, pre-op as ref						
Deteriorated	22/96 (22.9)	97/254 (38.2)	0.0071	3/23 (13.0)	21/58 (36.2)	0.040
New	12/22 (54.5)	61/97(62.9)		0/3 (0.0)	0/21 (0.0)	
Worsened	10/22 (45.5)	36/97 (37.1)		3/3 (100.0)	21/21 (100.0)	
Improved	20/96 (20.8)	43/254 (16.9)	0.40	13/23 (56.5)	25/58 (43.1)	0.28
Stable	50/96 (52.1)	113/254 (44.5)	0.20	6/23 (26.1)	12/58 (24.1)	0.60
3-month KPS status, pre-op as ref						
Deteriorated	37/96 (38.5)	122/256 (47.7)	0.13	9/23 (39.1)	24/60 (40.0)	0.94
Improved	16/96 (16.7)	40/256 (15.6)		5/23 (21.7)	20/60 (33.3)	0.30
Stable	43/96 (44.8)	94/256 (36.7)		9/23 (39.1)	16/60 (26.7)	0.60
6-month NIHSS-status, pre-op as ref						
Deteriorated	27/95 (28.4)	115/239 (48.1)	<0.0010	3/20 (15.0)	15/53 (28.3)	0.024
New	15/27 (55.6)	76/115 (66.1)		0/3 (0.0)	0/15 (0.0)	
Worsened	12/27 (44.4)	39/115 (33.9)		3/3 (100.0)	15/15 (100.0)	
Improved	20/95 (21.1)	37/239 (15.5)	0.22	13/20 (65.0)	22/53 (41.5)	0.073
Stable	48/95 (50.5)	87/239 (36.4)	<0.0001	4/20 (20.0)	16/53 (30.2)	0.38

eTable 2: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:3)			NIHSS score ≥ 2, matched (1:3)		
	Awake craniotomy (n = 107)	Asleep resection (n = 321)	*p* value	Awake craniotomy (n = 27)	Asleep resection (n = 81)	*p* value
6-month KPS status, pre-op as ref						
Deteriorated	43/96 (44.8)	134/241 (55.6)	0.073	7/20 (35.0)	21/53 (39.6)	0.72
Improved	14/96 (14.6)	32/241 (13.3)	0.75	5/20 (25.0)	16/53 (30.2)	0.66
Stable	39/96 (40.6)	75/241 (31.1)	0.096	8/20 (40.0)	16/53 (30.2)	0.36
Postoperative vascular complications			0.38			0.71
None	102/105 (97.1)	293/313 (93.6)		27/27 (100.0)	76/81 (93.8)	
Major ischemia	2/105 (1.9)	12/313 (3.8)		0/27 (0.0)	4/81 (5.2)	
Postoperative (reactive) bleeding	1/105 (1.0)	8/313 (2.6)		0/27 (0.0)	1/81 (1.3)	
Preoperative CE tumor volume, ml			0.011			0.52
Mean (SD)	38.8 (49.5)	51.5 (41.5)		36.0 (34.5)	40.6 (28.7)	
Median (Q1-Q3)	21.7 (10.6-49.6)	38.8 (20.0-71.1)		26.9 (18.2-36.1)	31.6 (23.2-51.7)	
Range	0.8-208.0	0.4-212.9		3.9-160.1	3.4-150.9	
Postoperative CE tumor volume, ml			<0.0001			0.048
Mean (SD)	2.0 (6.2)	6.9 (13.1)		1.2 (2.0)	3.7 (6.2)	
Median (Q1-Q3)	0.0 (0.0-1.0)	2.0 (0.02-6.8)		0.1 (0.0-1.7)	0.8 (0.0-4.8)	
Range	0.0-41.0	0.0-86.1		0.0-9.2	0.0-28.3	
Extent of resection CE tumor, % by volume			<0.0001			0.048
Mean (SD)	96.0 (8.0)	85.5 (19.8)		96.1 (6.4)	90.0 (14.9)	
Median (Q1-Q3)	100.0 (95.8-100.0)	94.1 (77.6-99.9)		99.7 (94.2-100.0)	98.0 (87.0-100.0)	
Range	48.2-100.0	23.1-100.0		71.4-100.0	45.8-100.0	
Median progression-free survival, months (95% CI)	9.5 (9.0-12.0)	8.0 (6.5-9.0)	0.0035	6.0 (4.0-13.0)	6.0 (4.8-8.0)	0.36
Median overall survival, months (95% CI)	18.0 (16.0-31.0)	14.0 (13.0-16.5)	<0.00047	10.0 (5.0-24.0)	8.5 (5.0-18.0)	0.23

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the matched NIHSS cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

eTable 3: Summary data for glioblastoma subgroups based on preoperative KPS

Characteristic	KPS 90-100, matched (1:3)			KPS ≤ 80, matched (1:3)		
	Awake craniotomy (n = 99)	Asleep resection (n = 297)	*p* value	Awake craniotomy (n = 35)	Asleep resection (n = 105)	*p* value
Center			<0.0001			0.018
Rotterdam	30/99 (30.3)	115/297 (38.7)		14/35 (40.0)	62/105 (59.0)	
The Hague	20/99 (20.2)	126/297 (42.4)		4/35 (11.4)	16/105 (15.2)	
Leuven	22/99 (22.2)	49/297 (16.5)		5/35 (14.3)	15/105 (14.3)	
Boston	27/99 (27.3)	7/297 (2.4)		12/35 (34.3)	12/105 (11.4)	
Year of surgery			0.53			0.90
2010-2015	28/99 (28.3)	94/297 (31.6)		14/35 (40.0)	40/105 (38.1)	
2016-2020	71/99 (71.7)	203/297 (68.4)		21/35 (60.0)	65/105 (61.9)	
Gender			0.49			0.79
Male	72/97 (72.7)	203/297 (68.4)		18/35 (51.4)	59/105 (56.2)	
Female	27/97 (27.3)	94/297 (31.6)		17/35 (48.6)	46/105 (43.8)	
Age at diagnosis, years			0.12			0.91
Mean (SD)	58.5 (12.7)	61.4 (11.4)		60.3 (12.5)	60.3 (10.9)	
Median (IQR)	59.0 (48.-66.0)	63.0 (54.0-70.0)		61.0 (54.0-68.5)	60.0 (53.0-69.0)	
Range	22.0-86.0	20.0-86.0		34.0-87.0	25.0-87.0	
Preoperative KPS			0.090			0.39
<60	0/97 (0.0)	0/297 (0.0)		1/35 (2.9)	1/105 (1.0)	
60	0/97 (0.0)	0/297 (0.0)		1/35 (2.9)	4/105 (3.8)	
70	0/97 (0.0)	0/297 (0.0)		6/35 (17.1)	28/105 (26.7)	
80	0/97 (0.0)	0/297 (0.0)		27/35 (77.1)	72/105 (68.6)	
90	65/97 (65.7)	223/297 (75.1)		0/35 (0.0)	0/105 (0.0)	
100	34/97 (34.3)	74/297 (24.9)		0.35 (0.0)	0/105 (0.0)	
Median preoperative KPS (IQR)	90 (90-100)	90 (90-90)		80 (80-80)	80 (70-80)	

eTable 3: Summary data for glioblastoma subgroups based on preoperative KPS

Characteristic	KPS 90-100, matched (1:3)			KPS ≤ 80, matched (1:3)		
	Awake craniotomy (n = 99)	Asleep resection (n = 297)	*p* value	Awake craniotomy (n = 35)	Asleep resection (n = 105)	*p* value
Preoperative ASA score			0.029			0.55
I	14/99 (14.1)	48/297 (16.2)		3/35 (8.6)	17/105 (16.2)	
II	48/99 (48.5)	193/297 (65.0)		15/35 (42.9)	64/105 (61.0)	
III	30/99 (30.3)	55/297 (18.5)		9/35 (25.7)	21/105 (20.0)	
IV	0/99 (0.0)	0/297 (0.0)		0/35 (0.0)	3/105 (2.9)	
Median preoperative ASA score (IQR)	2 (2-2)	2 (2-2)		2 (2-2)	2 (2-2)	
Preoperative NIHSS score			0.071			0.55
0	59/99 (59.6)	150/297 (50.5)		4/35 (11.4)	21/105 (20.0)	
1	29/99 (29.3)	91/297 (30.6)		15/35 (42.9)	32/105 (30.5)	
2	7/97 (7.1)	38/297 (12.8)		10/35 (28.6)	28/105 (26.7)	
3	1/99 (1.0)	12/297 (4.0)		2/35 (5.7)	11/105 (10.5)	
4	3/97 (3.0)	2/297 (0.7)		1/35 (2.9)	4/105 (3.8)	
>4	0/97 (0.0)	4/297 (1.4)		3/35 (8.6)	9/105 (8.6)	
Median preoperative NIHSS score (IQR)	0 (0-1)	0 (0-1)		1 (1-2)	1 (1-2)	
Tumor location by lobe			0.022			0.76
Frontal	37/97 (37.4)	80/297 (26.9)		14/35 (40.0)	40/105 (38.1)	
Parietal	24/97 (24.2)	80/297 (26.9)		9/35 (25.7)	20/105 (19.0)	
Temporal	35/97 (35.4)	114/297 (38.4)		12/35 (34.3)	38/105 (36.2)	
Occipital	1/97 (1.0)	23/297 (7.7)		0/35 (0.0)	7/105 (6.7)	
Insula	2/97 (2.0)	0/297 (0.0)		0/35 (0.0)	0/105 (0.0)	
Tumor location by hemisphere			<0.0001			0.90
Left	79/99 (79.8)	183/297 (61.6)		29/35 (82.9)	88/105 (83.8)	
Right	20/99 (20.2)	114/297 (38.4)		6/35 (17.1)	17/105 (16.2)	
Tumor location by eloquence			0.0051			0.10
Motor	47/97 (47.5)	148/297 (49.8)		14/35 (40.0)	48/105 (45.7)	
Sensory	3/97 (3.0)	11/297 (3.7)		1/35 (2.9)	2/105 (1.9)	
Language	53/97 (53.3)	118/297 (39.7)		23/35 (65.7)	49/105 (46.7)	
Visual	12/97 (12.1)	89/297 (30.0)		4/35 (11.4)	33/105 (31.4)	

eTable 3: Summary data for glioblastoma subgroups based on preoperative KPS

Characteristic	KPS 90-100, matched (1:3)			KPS ≤ 80, matched (1:3)		
	Awake craniotomy (n = 99)	Asleep resection (n = 297)	*p* value	Awake craniotomy (n = 35)	Asleep resection (n = 105)	*p* value
IDH status			0.34			0.89
Wildtype	75/86 (87.2)	177/193 (91.7)		26/26 (100.0)	62/64 (96.9)	
Mutant	11/86 (12.8)	16/193 (8.3)		0/26 (0.0)	2/64 (96.9)	
MGMT status			0.13	15/22 (68.2)	7/44 (15.9)	<0.0001
Methylated	27/67 (40.3)	56/192 (29.2)		7/22 (31.8)	37/44 (84.1)	
Unmethylated	40/67 (59.7)	136/192 (70.8)				
Surgical adjuncts						
Intraoperative ultrasound	21/99 (21.2)	16/297 (5.4)	<0.0001	7/35 (20.0)	19/105 (18.1)	0.80
Intraoperative fluorescence	24/99 (24.2)	61/297 (20.5)	0.53	5/35 (14.3)	16/105 (15.2)	0.89
Postoperative adjuvant therapy			0.057			
Radiotherapy only	3/97 (3.0)	21/297 (7.1)		0/35 (0.0)	8/105 (7.6)	
Chemotherapy only	3/97 (3.0)	1/297 (0.3)		0/35 (0.0)	0/105 (0.0)	
Chemoradiotherapy	89/97 (89.9)	260/297 (87.5)		33/35 (94.3)	93/105 (88.6)	
None	4/97 (4.0)	15/297 (5.1)		2/35 (5.7)	3/105 (2.9)	0.54
Reasons for no combined CTx + RTx			0.94			
Due to surgical deficits	1/10 (10.0)	6/37 (16.2)		0/2 (0.0)	1/11 (9.1)	
Due to rapid progression	2/10 (20.0)	6/37 (16.2)		1/2 (50.0)	3/11 (27.3)	
Pre-op already ineligible	6/10 (60.0)	20/37 (54.1)		0/2 (0.0)	5/11 (45.5)	
Patient's wish	1/10 (10.0)	6/37 (16.2)		0/2 (0.0)	2/11 (18.2)	
Due to inclusion in clinical trial	0/10 (0.0)	2/37 (5.4)		0/2 (0.0)	0/11 (0.0)	
Unknown	0/10 (0.0)	0/37 (0.0)		1/2 (50.0)	0/11 (0.0)	0.85

eTable 3: Summary data for glioblastoma subgroups based on preoperative KPS

Characteristic	KPS 90-100, matched (1:3)			KPS ≤ 80, matched (1:3)		
	Awake craniotomy (n = 99)	Asleep resection (n = 297)	*p* value	Awake craniotomy (n = 35)	Asleep resection (n = 105)	*p* value
6-week NIHSS-status, pre-op as ref						
Deteriorated	19/97 (20.7)	74/283 (26.1)	0.19	8/33 (24.2)	22/104 (21.2)	0.71
New	11/19 (57.9)	39/74 (52.7)		1/33 (3.0)	7/22 (31.9)	
Worsened	8/19 (42.1)	35/74 (47.3)		32/33 (97.0)	15/22 (68.2)	
Transient	4/19 (21.2)	6/74 (8.1)		1/33 (3.0)	3/22 (13.6)	
Permanent	15/19 (78.9)	68/74 (91.9)		32/33 (97.0)	19/22 (86.4)	
Improved	17/97 (17.5)	55/283 (19.4)	0.68	15/33 (45.5)	45/104 (43.3)	0.83
Stable	61/97 (62.9)	154/283 (54.4)	0.15	10/33 (30.3)	37/104 (35.6)	0.58
6-week KPS status, pre-op as ref						
Deteriorated	37/95 (38.9)	139/287 (48.4)	0.11	9/33 (27.3)	16/104 (15.4)	0.12
Improved	15/95 (15.8)	24/287 (8.4)	0.038	12/33 (36.4)	49/104 (47.1)	0.28
Stable	43/95 (45.3)	124/287 (43.2)	0.73	12/33 (36.4)	39/104 (37.5)	0.91
3-month NIHSS-status, pre-op as ref						
Deteriorated	17/88 (19.3)	74/237 (35.4)	0.034	8/31 (25.8)	27/90 (30.0)	0.66
New	12/17 (70.6)	39/74 (52.7)		0/8 (0.0)	9/27 (33.3)	
Worsened	5/17 (29.4)	35/74 (47.3)		8/8 (100.0)	18/27 (66.7)	
Improved	20/88 (22.7)	41/237(17.3)	0.27	13/31 (41.9)	36/90 (40.0)	0.85
Stable	48/88 (54.5)	111/237 (46.8)	0.061	8/31 (25.8)	26/90 (28.9)	0.67
3-month KPS status, pre-op as ref						
Deteriorated	38/88 (43.2)	135/237 (57.0)	0.027	8/31 (25.8)	13/93 (14.0)	0.15
Improved	10/88 (11.4)	16/237 (6.8)	0.17	11/31 (35.5)	46/93 (49.5)	0.18
Stable	40/88 (45.5)	86/237 (36.3)	0.13	12/31 (38.7)	34/93 (36.6)	0.83
6-month NIHSS-status, pre-op as ref						
Deteriorated	24/87 (27.6)	101/223 (45.3)	0.0043	5/28 (17.9)	34/88 (38.6)	0.043
New	15/24 (62.5)	64/101 (63.4)		0/5 (0.0)	9/34 (26.5)	
Worsened	9/24 (37.5)	37/101 (36.6)		5/5 (100.0)	25/34 (73.5)	
Improved	19/87 (21.8)	35/223 (15.7)	0.20	14/28 (50.0)	34/88 (38.6)	0.29
Stable	44/87 (50.6)	87/223 (39.0)	0.064	9/28 (32.1)	20/88 (22.7)	0.32

eTable 3: Summary data for glioblastoma subgroups based on preoperative KPS

Characteristic	KPS 90-100, matched (1:3)			KPS ≤ 80, matched (1:3)		
	Awake craniotomy (n = 99)	Asleep resection (n = 297)	*p* value	Awake craniotomy (n = 35)	Asleep resection (n = 105)	*p* value
6-month KPS status, pre-op as ref						
Deteriorated	44/88 (50.0)	145/224 (64.7)	0.017	7/29 (24.1)	21/88 (23.9)	0.98
Improved	9/88 (10.2)	13/224 (5.8)	0.17	10/29 (34.5)	40/88 (45.5)	0.30
Stable	35/88 (39.8)	66/224 (29.5)	0.080	12/29 (41.4)	27/88 (30.7)	0.29
Postoperative vascular complications			0.73			0.69
None	95/97 (97.9)	286/297 (96.3)		34/35 (97.1)	102/105 (97.1)	
Major ischemia	1/97 (1.0)	6/297 (2.0)		1/35 (2.9)	1/105 (1.0)	
Postoperative (reactive) bleeding	1/97 (1.0)	5/297 (1.7)		0/35 (0.0)	2/105 (2.0)	
Preoperative CE tumor volume, ml			0.021			0.54
Mean (SD)	36.3 (47.9)	47.8 (39.4)		43.8 (43.7)	48.5 (36.1)	
Median (Q1-Q3)	18.9 (10.3-43.4)	36.2 (19.8-62.9)		28.8 (16.2-55.4)	36.7 (23.9-64.7)	
Range	0.8-241.1	0.4-212.9		2.7-208.0	1.3-210.0	
Postoperative CE tumor volume, ml			<0.0001			0.0064
Mean (SD)	1.5 (4.9)	5.1 (9.7)		2.8 (7.3)	7.0 (12.2)	
Median (Q1-Q3)	0.0 (0.0-0.9)	1.5 (0.0-5.6)		0.3 (0.0-2.6)	1.8 (0.2-9.4)	
Range	0.0-41.0	0.0-72.7		0.0-40.0	0.0-81.7	
Extent of resection CE tumor, % by volume			<0.0001			0.014
Mean (SD)	96.8 (6.0)	87.3 (18.0)		94.0 (10.9)	84.2 (22.2)	
Median (Q1-Q3)	100.0 (95.6-100.0)	95.7 (81.9-100.0)		98.9 (92.9-100.0)	94.0 (77.8-99.3)	
Range	71.1-100.0	27.7-100.0		48.2-100.0	24.5-100.0	
Median progression-free survival, months (95% CI)	10.0 (9.0-13.0)	8.0 (7.0-9.0)	0.0010	8.0 (5.0-9.0)	6.5 (6.0-9.0)	0.73
Median overall survival, months (95% CI)	19.0 (16.0-31.0)	14.5 (13.0-16.5)	<0.00058	10.0 (9.0-37.0)	12.0 (11.5-16.8)	0.38

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the matched KPS cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

eTable 4: Factors independently predicting postoperative 6-week NIHSS deterioration ≥ 1 point (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Center														
Rotterdam	1.42 (0.21-9.80)	0.72	0.71 (0.09-5.37)	0.74	1.96 (0.85-2.07)	0.64	0.72 (0.09-5.60)	0.75	1.58 (0.09-28.6)	0.75	1.21 (0.07-19.8)	0.89	2.45 (0.18-32.9)	0.49
The Hague	1.00 (0.14-6.98)	1.00	0.65 (0.08-5.09)	0.68	0.81 (0.76-1.86)	0.89	0.52 (006-4.12)	0.53	0.87 (0.03-23.3)	0.93	1.00 (0.01-146)	1.00	1.10 (0.07-17.9)	0.95
Leuven	1.00 (0.13-7.61)	1.00	1.38 (0.15-12.6)	0.77	1.29 (0.19-1.39)	0.86	1.72 (0.16-19.0)	0.66	2.30 (0.08-69.8)	0.62	0.70 (0.04-11.2)	0.80	0.91 (0.04-22.2)	0.95
Boston	0.70 (0.09-5.31)	0.73	1.60 (0.18-14.2)	0.67	0.47 (0.25-1.50)	0.64	1.62 (0.18-14.4)	0.67	0.21 (0.0-12.0)	0.44	1.18 (0.06-24.2)	0.91	0.39 (0.02-6.94)	0.51
Year of surgery														
2010-2015	0.98 (0.06-16.8)	0.99	1.12 (0.06-19.8)	0.94	0.67 (0.63-1.72)	0.81	0.95 (0.05-16.6)	0.97	0.69 (0.03-18.1)	0.82	2.42 (0.04-14.3)	0.67	1.26 (0.06-25.3)	0.88
2016-2020	1.02 (0.06-17.6)	0.99	0.89 (0.05-15.7)	0.94	1.48 (0.40-1.58)	0.81	1.06 (0.06-18.5)	0.97	1.44 (0.06-37.7)	0.82	0.41 (0.01-24.4)	0.67	0.80 (0.04-16.)	0.88
Gender														
Male	0.91 (0.62-1.33)	0.62	0.80 (0.43-1.48)	0.47	0.83 (0.79-1.86)	0.86	1.03 (0.57-1.86)	0.91	0.54 (0.06-5.12)	0.58	1.34 (0.41-4.43)	0.63	0.44 (0.11-1.72)	0.23
Female	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Age at diagnosis	1.00 (0.98-1.02)	0.78	1.02 (0.99-1.06)	0.19	1.08 (0.71-1.38)	0.49	1.01 (0.99-10.4)	0.28	1.00 (0.91-1.10)	0.98	1.01 (0.95-1.07)	0.75	0.99 (0.92-1.05)	0.65
Preoperative KPS														
90-100	0.71 (0.04-12.5)	0.81	0.76 (0.04-13.6)	0.85	0.53 (0.49-1.57)	0.70	0.75 (0.04-13.5)	0.85	1.29 (0.05-33.3)	0.88	NA		NA	
≤ 80	1.41 (0.08-24.9)	0.81	1.32 (0.07-23.7)	0.85	1.89 (0.78-2.02)	0.70	1.33 (0.07-23.8)	0.85	0.77 (0.03-20.0)	0.88	NA		NA	

eTable 4: Factors independently predicting postoperative 6-week NIHSS deterioration ≥ 1 point (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	Overall [n= 1047]		<70 [n=625]		≥ 70 [n=422]		NIHSS 0-1 [n=621]		NIHSS ≥ 2 [n=426]		KPS 90-100 [n=492]		KPS ≤ 80 [n=555]	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative ASA score														
I	0.37 (0.11-1.29)	0.12	0.61 (0.12-3.12)	0.55	0.84 (0.78-1.90)	0.91	0.70 (0.14-3.64)	0.67	0.32 (0.01-9.37)	0.50	0.50 (0.05-5.20)	0.58	0.57 (0.04-7.23)	0.66
II	0.48 (0.15-1.54)	0.22	0.64 (0.13-3.07)	0.58	1.16 (0.09-2.22)	0.92	0.75 (0.16-3.57)	0.72	1.21 (0.07-21.9)	0.89	0.78 (0.09-6.57)	0.82	0.35 (0.03-3.62)	0.37
III	0.52 (0.17-1.62)	0.26	0.68 (0.14-3.18)	0.62	1.15 (0.14-1.89)	0.92	0.47 (0.10-2.19)	0.33	2.25 (0.10-53.2)	0.61	1.29 (0.13-12.5)	0.83	1.25 (0.12-13.0)	0.85
IV	NA		NA		NA		NA		NA		NA		NA	
Preoperative NIHSS score														
0-1	1.73 (0.09-31.8)	0.71	2.20 (0.11-45.0)	0.61	1.95 (0.81-2.08)	0.70	NA		NA		3.79 (0.12-17.31)	0.44	3.77 (0.12-114)	0.44
≥ 2	0.58 (0.03-10.6)	0.71	0.45 (0.02-9.27)	0.61	0.51 (0.45-1.55)	0.70	NA		NA		0.26 (0.01-8.16)	0.44	0.27 (0.01-8.04	0.44
Tumor location by lobe														
Frontal	1.10 (0.24-5.05)	0.90	0.77 (0.10-5.72)	0.79	0.93 (0.88-1.98)	0.96	0.64 (0.09-4.86)	0.67	2.57 (0.14-46.2)	0.51	1.03 (0.11-9.74)	0.98	1.04 (0.09-11.8)	0.97
Parietal	1.19 (0.26-5.48)	0.82	1.31 (0.18-9.71)	0.79	2.56 (0.42-2.71)	0.52	1.11 (0.15-8.34)	0.92	3.52 (0.22-56.5)	0.36	1.94 (0.20-18.5)	0.56	0.96 (0.08-11.6)	0.98
Temporal	1.13 (0.25-5.21)	0.87	0.47 (0.06-3.53)	0.47	0.55 (0.52-1.58)	0.67	0.50 (0.07-3.75)	0.50	0.20 (0.01-4.72)	0.31	0.63 (0.07-6.05)	0.68	2.08 (0.20-22.1)	0.54
Occipital	1.33 (0.26-6.72)	0.73	2.16 (0.23-20.2)	0.50	0.77 (0.43-1.84)	0.90	3.33 (0.36-31.1)	0.29	0.41 (0.01-12.6)	0.60	0.80 (0.05-12.7)	0.88	0.40 (0.01-12.9)	0.60
Insula	NA		NA		NA		NA		NA		NA		NA	

eTable 4: Factors independently predicting postoperative 6-week NIHSS deterioration ≥ 1 point (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Tumor location by hemisphere														
Left	1.17 (0.77-1.79)	0.47	0.97 (0.47-2.03)	0.94	0.30 (0.11-1.45)	0.29	0.76 (0.38-1.54)	0.45	0.20 (0.01-2.82)	0.22	0.96 (0.24-3.75)	0.95	2.97 (0.56-15.7)	0.19
Right	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Tumor location by eloquence														
Motor	1.54 (0.90-2.65)	0.12	3.98 (1.63-9.70)	0.002	1.53 (0.46-2.61)	0.75	1.44 (0.55-3.74)	0.45	2.89 (1.68-49.7)	0.018	1.55 (0.27-8.96)	0.62	13.8 (1.20-160)	0.033
Sensory	1.59 (0.59-4.28)	0.36	0.88 (0.13-5.79	0.89	0.98 (0.88-1.07)	0.99	0.58 (0.08-4.03)	0.58	1.14 (0.01-110)	0.96	0.24 (0.01-7.94)	0.41	2.80 (0.07-114)	0.58
Language	1.68 (0.90-3.11)	0.10	5.30 (1.92-14.6)	0.001	0.76 (0.72-1.79)	0.83	1.96 (0.67-5.68)	0.22	12.4 (0.76-203)	0.070	3.81 (0.54-26.8)	0.17	8.55 (0.53-138)	0.13
Visual	1.78 (1.07-2.95)	0.026	2.65 (1.15-6.09)	0.022	0.53 (0.23-1.45)	0.64	1.80 (0.80-4.04)	0.15	2.42 (0.24-24.2)	0.44	2.52 (0.54-11.7)	0.23	10.2 (1.54-67.6)	0.015
IDH status														
Wildtype	0.67 (0.10-2.31)	0.56	0.56 (0.02-2.75)	0.52	1.00 (0.01-15.9)	1.00	1.00 (0.14-4.47)	1.00	1.00 (0.01-168)	1.00	1.20 (0.18-5.63)	0.81	1.00 (0.01-154)	1.00
Mutant	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
MGMT status														
Methylated	1.25 (0.77-2.07)	0.36	0.89 (0.41-1.85)	0.75	1.04 (0.23-4.75)	0.95	1.29 (0.63-2.80)	0.49	1.37 (0.23-8.21)	0.72	1.78 (0.76-5.02)	0.21	0.48 (0.12-2.02)	0.31
Unmethylated	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Awake craniotomy	0.73 (0.39-1.37)	0.33	0.61 (0.28-1.35)	0.22	0.66 (0.23-1.45)	0.70	0.68 (0.31-1.47)	0.32	0.28 (0.02-3.57)	0.32	0.31 (0.05-1.92)	0.20	1.29 (0.29-5.66)	0.73

eTable 4: Factors independently predicting postoperative 6-week NIHSS deterioration ≥ 1 point (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Intraoperative ultrasound	0.84 (0.47-1.52)	0.56	0.92 (0.37-2.31)	0.86	1.48 (0.34-1.88)	0.79	0.68 (0.27-1.70)	0.41	1.88 (0.12-30.2)	0.65	0.57 (0.06-5.73)	0.63	1.85 (0.31-11.0)	0.49
Intraoperative fluorescence	1.09 (0.47-2.54)	0.83	0.90 (0.23-3.48)	0.88	1.29 (0.20-2.40)	0.89	0.80 (0.14-4.66)	0.81	0.99 (0.04-24.6)	1.00	2.33 (0.37-14.5)	0.36	0.44 (0.02-9.79)	0.60
6-week KPS, pre-op as ref														
Deteriorated	7.62 (5.13-11.3)	<0.0001	8.42 (4.51-15.7)	<0.0001	17.7 (6.91-18.5)	<0.0001	8.52 (4.71-15.4)	<0.0001	42.2 (2.65-671)	<0.0001	8.07 (2.31-28.3)	<0.0001	0.85 (0.79-0.92)	0.0010
Postoperative vascular complications														
None	0.81 (0.09-6.99)	0.85	0.71 (0.05-10.7)	0.81	1.01 (0.92-1.12)	1.00	0.54 (0.05-6.51)	0.63	0.87 (0.02-33.9)	0.94	0.51 (0.03-9.00)	0.64	1.82 (0.08-42.5)	0.71
Major ischemia	4.93 (0.56-43.2)	0.15	10.8 (0.62-189)	0.10	0.99 (0.89-1.09)	1.00	3.46 (0.26-46.3)	0.35	128 (0.63-Inf)	0.066	4.05 (0.11-143.4)	0.43	2.09 (0.06-67.9)	0.67
Postop bleeding	1.11 (0.13-9.50)	0.93	0.27 (0.01-5.11)	0.38	1.00 (0.91-1.10)	1.00	0.63 (0.05-8.74)	0.73	0.21 (0.00-15.1)	0.47	0.67 (0.03-14.2)	0.80	0.14 (0.00-7.00)	0.32

eTable 4: Factors independently predicting postoperative 6-week NIHSS deterioration ≥ 1 point (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative CE tumor volume														
0-10 ml	0.59 (0.10-3.48)	0.56	0.45 (0.07-3.11)	0.42	0.23 (0.11-1.45)	0.45	0.50 (0.08-3.30)	0.47	0.59 (0.01-33.0)	0.79	0.27 (0.03-2.76)	0.26	3.37 (0.20-58.2)	0.40
10-25 ml	1.61 (0.29-8.85)	0.58	2.61 (0.44-15.7)	0.29	1.47 (0.40-1.87)	0.77	1.65 (0.28-9.67)	0.58	0.70 (0.04-12.5)	0.81	1.86 (0.24-14.7)	0.55	0.79 (0.09-7.03)	0.83
25-50 ml	1.08 (0.20-5.88)	0.93	1.00 (0.17-5.87)	1.00	1.55 (0.70-2.08)	0.20	1.11 (0.19-6.36(	0.91	3.28 (0.21-51.4)	0.39	1.83 (0.23-14.6)	0.56	1.40 (0.17-11.7)	0.76
50-100 ml	0.86 (0.16-4.69)	0.86	1.12 (0.19-6.73)	0.90	0.89 (0.84-0.95)	0.94	1.06 (0.18-6.13)	0.95	1.05 (0.06-19.3)	0.97	1.12 (0.12-10.3)	0.92	0.81 (0.10-6.80)	0.84
>100 ml	1.11 (0.20-6.21)	0.91	0.80 (0.12-5.20)	0.82	0.46 (0.22-1.51)	0.70	0.98 (0.16-6.15)	0.99	0.66 (0.06-18.9)	0.84	0.75 (0.04-12.6)	0.84	0.38 (0.03-5.43)	0.47
Postoperative CE tumor volume														
0-0.2 ml	1.08 (0.16-7.57)	0.94	0.90 (0.15-5.57)	0.91	0.87 (0.42-1.37)	0.93	0.49 (0.06-3.94)	0.50	1.10 (0.06-18.9)	0.95	0.61 (0.05-7.50)	0.70	0.78 (0.06-10.4)	0.85
0.2-1.0 ml	1.09 (0.16-7.46)	0.93	1.78 (0.29-11.0)	0.53	0.90 (0.83-1.12)	0.95	1.19 (0.15-9.15)	0.87	0.48 (0.03-8.44	0.61	0.96 (0.09-9.91)	0.97	0.45 (0.04-5.49)	0.52
1.0-2.0 ml	0.99 (0.14-6.79)	0.99	1.51 (0.24-9.72)	0.66	0.88 (0.56-1.39)	0.93	1.04 (0.13-8.08)	0.97	0.97 (0.06-15.9)	0.98	1.19 (0.10-14.9)	0.89	3.30 (0.26-42.4)	0.35
>2.0 ml	0.86 (0.12-6.00)	0.88	3.52 (0.49-25.6)	0.21	1.46 (0.85-1.20)	0.81	1.62 (0.20-13.3)	0.65	2.02 (0.09-47.2)	0.65	1.41 (0.11-17.8)	0.79	0.99 (0.08-12.7)	0.99

eTable 4: Factors independently predicting postoperative 6-week NIHSS deterioration ≥ 1 point (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Extent of resection CE tumor														
98-100 %	1.03 (0.18-6.03)	0.97	1.66 (0.23-12.0)	0.62	1.10 (0.94-1.17)	0.95	1.88 (0.26-13.5)	0.53	1.22 (0.05-28.0)	0.90	2.49 (0.19-32.5)	0.48	1.98 (0.16-24.8)	0.59
95-98 %	0.94 (0.17-0.25)	0.94	0.95 (0.14-6.27)	0.96	0.88 (0.80-1.16)	0.95	1.10 (0.17-7.02)	0.92	0.78 (0.01-54.1)	0.91	1.56 (0.14-18.0)	0.72	0.58 (0.05-7.16)	0.67
90-95 %	0.98 (0.18-5.42)	0.99	1.40 (0.23-8.59)	0.72	0.46 (0.22-1.34)	0.59	0.97 (0.16-5.98)	0.98	4.63 (0.26-82.8)	0.29	1.09 (0.10-11.5)	0.94	1.37 (0.15-12.7)	0.78
80-90 %	0.79 (0.14-4.48)	0.79	0.47 (0.07-3.18)	0.44	0.82 (0.47-1.53)	0.89	0.56 (0.09-3.64)	0.54	0.14 (0.00-5.50)	0.29	0.29 (0.02-4.99)	0.38	0.22 (0.01-3.80)	0.29
<80 %	1.33 (0.24-7.41)	0.74	0.94 (0.15-6.01)	0.95	3.04 (0.85-4.41)	0.49	0.90 (0.14-5.64)	0.91	1.02 (0.04-27.4)	0.99	0.70 (0.07-7.28)	0.76	1.99 (0.20-20.0)	0.55
Interaction	1.01 (0.87-1.01)	0.71	1.02 (0.45-1.36)	0.98	1.21 (0.89-1.32)	0.76	1.11 (0.79-1.34)	0.37	1.42 (0.74-1.33)	0.84	1.25 (0.56-1.45)	0.75	1.00 (0.16-1.23)	0.60
Awake*age	1.15 (0.74-1.15)	0.86	1.06 (0.65-1.34)	0.97	1.18 (0.47-1.62)	0.42	1.31 (0.76-1.49)	0.82	1.21 (0.89-1.33)	0.93	1.05 (0.66-1.23)	0.68	1.01 (0.55-1.52)	0.73
Awake*NIHSS	0.72 (0.61-1.21)	0.60	0.98 (0.34-1.77)	0.99	1.27 (0.39-2.33)	0.51	0.89 (0.54-1.12)	0.95	1.08 (0.68-1.52)	0.42	0.89 (0.23-1.84)	0.94	0.64 (0.26-1.89)	0.37
Awake*KPS														

eTable 5: Factors independently predicting postoperative 6-week KPS deterioration ≥ 10 points (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Center														
Rotterdam	1.07 (0.16-7.33)	0.96	1.41 (0.19-10.6)	0.74	0.68 (0.03-15.4)	0.78	0.99 (0.13-7.39)	0.99	0.75 (0.06-10.2)	0.83	1.09 (0.08-15.7)	0.95	0.14 (0.01-2.62)	0.18
The Hague	0.77 (0.11-5.31)	0.75	1.71 (0.22-13.0)	0.60	0.49 (0.02-13.3)	0.63	1.07 (0.14-8.19)	0.95	0.85 (0.05-15.5)	0.91	1.00 (0.01-14.7)	1.00	0.83 (0.04-15.6)	0.90
Leuven	1.79 (0.24-13.4)	0.52	0.78 (0.09-7.03)	0.83	1.02 (0.05-2.31)	0.32	1.96 (0.20-19.3)	0.56	1.53 (0.06-39.9)	0.79	1.33 (0.09-20.5)	0.83	3.93 (0.09-168)	0.47
Boston	0.69 (0.09-5.08)	0.71	0.51 (0.06-4.42)	0.54	0.93 (0.03-26.8)	0.96	0.48 (0.06-4.16)	0.51	1.07 (0.06-18.9)	0.96	0.68 (0.04-11.8)	0.79	1.78 (0.08-37.3)	0.71
Year of surgery														
2010-2015	1.04 (0.06-17.9)	0.97	0.98 (0.06-17.1)	0.99	0.66 (0.01-32.3)	0.81	0.98 (0.06-17.1)	0.99	0.65 (0.03-14.3)	0.78	0.29 (0.01-17.2)	0.55	1.06 (0.05-22.1)	0.97
2016-2020	0.96 (0.06-16.5)	0.97	1.02 (0.06-17.8)	0.99	1.52 (0.03-74.8)	0.81	1.02 (0.06-17.8)	0.99	1.55 (0.07-34.2)	0.78	3.40 (0.06-19.9)	0.55	0.94 (0.05-19.5)	0.97
Gender														
Male	1.18 (0.84-1.67)	0.55	1.06 (0.62-1.83)	0.83	0.97 (0.13-7.12)	0.98	0.82 (0.47-1.43)	0.49	4.56 (0.44-18.9)	0.032	3.59 (0.07-12.0)	0.67	1.04 (0.22-4.93)	0.96
Female	Ref		Ref		Ref		Ref		Ref		Ref		Ref	Ref
Age at diagnosis	1.03 (1.01-1.05)	<0.001	1.01 (0.98-1.03)	0.61	1.08 (0.84-1.38)	0.50	1.03 (1.00-1.05)	0.052	1.04 (0.98-1.12)	0.20	1.02 (0.97-1.07)	0.43	1.13 (1.03-1.24)	0.007
Preoperative KPS														
90-100	1.91 (0.10-36.1)	0.66	2.21 (0.11-44.5)	0.60	2.57 (0.06-14.6)	0.58	1.90 (0.10-36.7)	0.67	1.43 (0.07-30.4)	0.82	NA		NA	
≤ 80	0.52 (0.03-9.85)	0.66	0.45 (0.02-9.12)	0.60	0.39 (0.01-17.4)	0.58	0.53 (0.03-10.2)	0.67	0.70 (0.03-14.9)	0.82	NA		NA	

eTable 5: Factors independently predicting postoperative 6-week KPS deterioration ≥ 10 points (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative ASA score														
I	1.09 (0.36-3.32)	0.87	0.54 (0.12-2.45)	0.43	0.93 (0.03-28.1)	0.96	0.19 (0.04-0.99)	0.048	6.1 (2.14-Inf)	0.014	1.54 (0.19-12.4)	0.68	3.86 (0.17-85.9)	0.39
II	1.11 (0.40-3.07)	0.85	0.42 (0.10-1.75)	0.23	0.45 (0.03-7.70)	0.53	0.25 (0.05-1.14)	0.073	3.01 (0.22-40.8)	0.40	0.41 (0.07-2.42)	0.31	12.3 (0.85-177)	0.062
III	1.41 (0.52-3.83)	0.50	0.43 (0.10-1.78_)	0.25	1.53 (0.09-27.5)	0.74	0.49 (0.11-2.17)	0.35	1.69 (0.13-21.5)	0.68	0.87 (1.13-6.07)	0.89	1.92 (0.20-18.8)	0.57
IV	NA		NA		NA		NA		NA		NA		NA	
Preoperative NIHSS score														
0-1	0.92 (0.05-15.8)	0.95	0.74 (0.04-13.3)	0.84	0.55 (0.01-24.0)	0.72	NA		NA		0.68 (0.03-14.1)	0.80	0.45 (0.02-11.2)	0.63
≥ 2	1.09 (0.06-18.7)	0.95	1.35 (0.08-24.1)	0.84	1.83 (0.04-80.5)	0.72	NA		NA		1.48 (0.07-30.7)	0.80	2.20 (0.09-54.5)	0.63
Tumor location by lobe														
Frontal	0.76 (0.16-3.48)	0.72	1.49 (0.21-10.6)	0.69	2.07 (0.09-50.1)	0.61	1.64 (0.22-12.3)	0.63	1.86 (0.16-21.5)	0.61	0.78 (0.09-6.88)	0.82	1.50 (0.13-17.6)	0.74
Parietal	0.84 (0.18-3.86)	0.82	1.07 (0.15-7.56)	0.95	0.66 (0.03-15.6)	0.77	1.01 (0.13-7.51)	0.99	0.52 (0.05-5.43)	0.57	0.65 (0.07-5.79)	0.69	0.72 (0.06-9.29)	0.80
Temporal	0.79 (0.17-3.64)	0.76	1.15 (0.16-8.14)	0.89	2.59 (0.11-61.0)	0.50	1.60 (0.22-11.8)	0.65	0.61 (0.06-6.60)	0.68	0.94 (0.11-8.36)	0.95	0.84 (0.07-9.57)	0.89
Occipital	0.63 (0.13-3.14)	0.57	0.53 (0.06-4.54)	0.56	0.15 (0.00-12.7)	0.35	0.31 (0.03-3.04)	0.32	1.75 (0.12-24.8)	0.67	2.35 (0.18-30.5)	0.51	1.13 (0.04-33.0)	0.94
Insula	NA		NA		NA		NA		NA		NA		NA	

eTable 5: Factors independently predicting postoperative 6-week KPS deterioration ≥ 10 points (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Tumor location by hemisphere														
Left	1.28 (0.87-1.89)	0.20	0.94 (0.50-1.75)		3.58 (0.26-48.6)	0.28	1.64 (0.87-3.09)	0.13	2.05 (0.31-13.6)	0.44	1.46 (0.42-5.09)	0.54	1.32 (0.22-7.82)	0.76
Right	Ref		Ref		Ref		Ref	0.83	Ref		Ref		Ref	
Tumor location by eloquence														
Motor	1.07 (0.66-1.76)	0.77	1.03 (0.50-2.14)	0.93	3.65 (0.17-76.9)	0.34	0.91 (0.38-2.17)	0.83	0.51 (0.07-3.56)	0.48	4.75 (0.87-26.1)	0.068	0.76 (0.07-8.08)	0.82
Sensory	1.16 (0.50-2.71)	0.74	0.83 (0.21-3.30)	0.79	0.22 (0.00-22.9)	0.46	0.58 (0.12-2.68)	0.48	1.71 (0.05-54.4)	0.76	2.37 (0.14-39.0)	0.54	0.72 (0.02-23.4)	0.85
Language	0.84 (0.48-1.48)	0.55	0.77 (0.32-1.83)	0.55	0.72 (0.03-17.4)	0.82	0.53 (0.20-1.39)	0.19	1.37 (0.15-12.7)	0.78	6.40 (0.89-46.2)	0.061	0.39 (0.03-4.68)	0.46
Visual	0.93 (0.59-1.49)	0.77	1.19 (0.58-2.44)	0.63	0.11 (0.00-2.36)	0.11	0.79 (0.37-1.70)	0.55	0.39 (0.06-2.62)	0.32	1.78 (0.45-7.03)	0.40	0.15 (0.02-1.27)	0.078
IDH status														
Wildtype	0.73 (0.19-2.09)	0.58	1.02 (0.21-4.11)	0.98	1.00 (0.01-15.8)	1.00	1.30 (0.32-5.44)	0.69	1.00 (0.01-168)	1.00	1.00 (0.24-3.79)	1.00	1.00 (0.01-154)	1.00
Mutant	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
MGMT status														
Methylated	1.34 (0.90-2.03)	0.16	1.25 (0.67-2.37)	0.48	0.81 (0.23-2.89)	0.74	1.64 (0.89-3.21)	0.12	1.53 (0.35-6.65)	0.55	1.69 (0.87-3.50)	0.13	0.28 (0.06-1.29)	0.093
Unmethylated	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Awake craniotomy	1.07 (0.63-1.74)	0.80	0.87 (0.45-1.68)	0.68	1.10 (0.08-15.6)	0.93	0.80 (0.40-1.60)	0.53	0.63 (0.12-3.32)	0.58	3.82 (0.74-19.8)	0.10	3.63 (0.68-19.5)	0.13

eTable 5: Factors independently predicting postoperative 6-week KPS deterioration ≥ 10 points (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Intraoperative ultrasound	1.05 (0.63-1.74)	0.86	1.31 (0.57-3.03)	0.53	0.74 (0.03-25.8)	0.82	1.04 (0.42-2.57)	0.93	0.45 (0.06-3.16)	0.41	0.92 (0.12-7.16)	0.93	2.90 (0.46-18.2)	0.25
Intraoperative fluorescence	1.14 (0.53-2.44)	0.74	1.72 (0.69-4.28)	0.25	1.02 (0.05-2.69)	0.32	0.97 (0.22-4.32)	0.96	5.69 (0.22-149)	0.28	1.28 (0.20-8.17)	0.79	3.89 (0.09-166)	0.47
6-week NIHSS, pre-op as ref														
Deteriorated	7.46 (5.02-11.1)	<0.0001	8.86 (4.74-16.5)	<0.0001	25.2 (1.96-662)	<0.0001	9.21 (5.02-16.9)	<0.0001	5.19 (3.88-69.5)	0.0020	7.38 (2.24-24.4)	0.0010	47.1 (6.53-340)	0.0010
Postoperative vascular complications														
None	0.53 (0.05-6.03)	0.61	0.54 (0.03-8.75)	0.66	2.12 (0.01-301)	0.74	0.38 (0.03-4.90)	0.46	0.98 (0.03-28.1)	0.99	0.89 (0.03-23.5)	0.94	0.12 (0.00-11.5)	0.36
Major ischemia	0.57 (0.05-6.60)	0.65	0.50 (0.08-8.43)	0.63	0.47 (0.00-66.9)	0.74	0.80 (0.06-10.9)	0.87	0.54 (0.01-22.1)	0.74	0.14 (0.00-7.25)	0.32	0.91 (0.01-90.9)	0.97
Postop bleeding	5.33 (0.39-72.0)	0.21	9.84 (0.54-178)	0.12	1.00 (0.00-262)	1.00	4.15 (0.3-74.2)	0.33	1.94 (0.04-104)	0.74	23.1 (0.36-Inf)	0.13	35.6 (0.23-Inf)	0.16

eTable 5: Factors independently predicting postoperative 6-week KPS deterioration ≥ 10 points (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative CE tumor volume														
0-10 ml	1.11 (0.20-6.20)	0.90	1.63 (0.28-9.37	0.58	0.73 (0.02-25.1)	0.84	1.28 (0.21-7.86)	0.79	2.05 (0.14-29.3)	0.59	1.73 (0.18-16.9)	0.63	0.99 (0.08-13.0)	0.46
10-25 ml	0.80 (0.15-429)	0.79	0.71 (0.13-3.79)	0.68	1.92 (0.11-33.4)	0.61	0.90 (0.16-5.09)	0.91	0.91 (0.10-8.41)	0.94	0.58 (0.08-4.51)	0.60	1.60 (0.17-15.1)	0.68
25-50 ml	0.90 (0.17-4.79)	0.90	0.91 (0.17-4.83)	0.91	0.17 (0.00-5.73)	0.26	0.83 (0.15-4.63	0.83	0.39 (0.04-3.57)	0.39	0.56 (0.07-4.53)	0.58	0.62 (0.07-5.60)	0.67
50-100 ml	1.10 (0.21-5.85)	0.91	1.05 (0.19-5.68)	0.95	2.43 (0.12-47.7)	0.51	0.85 (0.15-4.81)	0.86	1.70 (0.16-17.5)	0.65	0.56 (0.06-5.24)	0.60	1.12 (0.12-10.4)	0.92
>100 ml	1.14 (0.21-6.26)	0.88	1.38 (0.24-8.04)	0.72	1.06 (0.02-63.6)	0.97	1.24 (0.21-7.44)	0.82	0.79 (0.03-19.5)	0.88	9.15 (0.23-368)	0.23	0.89 (0.03-24.2)	0.94
Postoperative CE tumor volume														
0-0.2 ml	0.84 (0.12-5.78)	0.86	1.16 (0.17-7.77)	0.88	0.70 (0.02-21.8)	0.82	1.07 (0.14-8.23)	0.95	0.33 (0.02-4.93)	0.41	0.35 (0.02-4.91)	0.42	0.37 (0.03-5.42)	0.46
0.2-1.0 ml	0.93 (0.14-6.29)	0.94	0.90 (0.14-5.82)	0.91	0.49 (0.01-23.4)	0.68	0.71 (0.10-5.17)	0.73	0.30 (0.02-4.29)	0.36	0.80 (0.09-8.02)	0.85	0.61 (0.04-9.35)	0.72
1.0-2.0 ml	1.22 (0.18-8.28)	0.84	1.69 (0.26-11.1)	0.59	1.29 (0.06-26.3)	0.85	1.14 (0.15-8.49)	0.90	2.21 (0.16-30.6)	0.54	1.27 (0.09-16.9)	0.86	1.35 (0.09-19.4)	0.82
>2.0 ml	1.05 (0.15-7.24)	0.96	1.01 (0.15-6.93)	0.99	2.05 (0.08-50.1)	0.62	1.16 (0.15-8.86)	0.89	6.44 (0.31-133)	0.22	2.82 (0.23-35.0)	0.41	3.72 (0.23-60.8)	0.35

eTable 5: Factors independently predicting postoperative 6-week KPS deterioration ≥ 10 points (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Extent of resection CE tumor														
98-100 %	0.86 (0.15-4.93)	0.87	0.90 (0.14-5.90)	0.91	1.24 (0.04-38.3)	0.89	0.87 (0.13-5.84)	0.88	1.28 (0.10-17.2)	0.85	2.83 (0.22-36.2)	0.42	0.79 (0.06-10.0)	0.85
95-98 %	0.74 (0.13-4.09)	0.73	0.64 (0.10-3.88)	0.62	0.29 (0.00-30.0)	0.55	0.86 (0.14-5.20)	0.87	0.27 (0.01-5.29)	0.38	0.35 (0.03-4.24)	0.40	1.83 (0.13-25.0)	0.65
90-95 %	1.34 (0.25-7.32)	0.73	1.14 (0.19-6.75)	0.88	1.73 (0.09-34.1)	0.68	1.03 (0.17-6.11)	0.98	1.35 (0.13-13.9)	0.79	1.34 (0.14-12.4)	0.80	1.01 (0.09-11.3)	1.00
80-90 %	1.15 (0.21-6.34)	0.87	1.63 (0.27-9.92)	0.59	4.26 (0.10-174)	0.38	1.26 (0.21-7.65)	0.80	3.56 (0.31-41.1)	0.30	1.07 (0.10-11.0)	0.95	0.39 (0.03-5.51)	0.48
<80 %	1.01 (0.18-5.57)	0.99	0.94 (0.16-5.70)	0.95	0.30 (0.01-10.7)	0.45	1.04 (0.17-6.23)	0.97	0.52 (0.04-7.16)	0.62	0.71 (0.08-6.58	0.76	1.64 (0.14-19.8)	0.69
Interaction	1.00 (1.00-1.00)	0.81	0.88 (0.54-1.23)	0.78	0.97 (0.73-1.24)	0.98	1.33 (0.76-1.42)	0.88	1.02 (0.67-1.32)	0.76	1.01 (0.33-1.24)	0.64	0.77 (0.23-1.62)	0.82
Awake*age	0.82 (0.63-1.23)	0.74	0.69 (0.84-1.58)	0.52	0.99 (0.96-1.11)	0.79	1.02 (0.88-1.38)	0.75	0.81 (0.21-1.82)	0.92	0.65 (0.21-1.45)	0.50	0.46 (0.73-1.23)	0.61
Awake*NIHSS	0.71 (0.55-1.45)	0.56	1.22 (0.45-1.98)	0.40	1.04 (0.93-1.07)	0.68	0.85 (0.66-1.31)	0.84	1.13 (0.56-1.90)	0.67	1.12 (0.45-1.61)	0.98	0.73 (0.77-1.44)	0.98
Awake*KPS														

eTable 6: Factors independently predicting receival of adjuvant chemoradiotherapy (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Center														
Rotterdam	0.17 (0.02-1.74)	0.14	0.18 (0.02-1.85)	0.15	0.16 (0.01-2.74)	0.20	0.19 (0.02-2.13)	0.18	0.12 (0.01-1.56)	0.10	0.13 (0.01-1.59)	0.11	0.16 (0.01-1.71)	0.13
The Hague	2.11 (0.74-2.38)	0.47	2.13 (0.44-3.73)	0.14	2.69 (0.08-90.9)	0.58	1.03 (0.44-3.82)	0.14	1.31 (0.39-4.37)	0.15	3.77 (0.26-227)	0.24	1.99 (0.60-65.9)	0.093
Leuven	0.70 (0.06-7.63)	0.77	0.81 (0.07-9.12)	0.86	0.68 (0.03-15.0)	0.81	0.49 (0.04-6.42)	0.59	0.62 (0.04-9.65)	0.73	0.67 (0.05-9.38)	0.76	0.84 (0.07-10.7)	0.90
Boston	1.44 (0.14-15.1)	0.76	1.23 (1.11-13.5)	0.87	3.20 (0.08-120)	0.53	1.92 (0.16-23.4)	0.61	1.75 (0.13-22.7)	0.67	1.75 (0.12-25.8)	0.68	1.21 (0.11-13.7)	0.88
Year of surgery														
2010-2015	0.65 (0.04-11.8)	0.77	0.83 (0.05-14.7)	0.90	0.97 (0.05-19.5)	0.98	0.68 (0.04-12.4)	0.79	0.56 (0.03-11.1)	0.70	0.82 (0.04-15.3)	0.90	0.54 (0.03-10.5)	0.69
2016-2020	1.54 (0.08-27.8)	0.77	1.21 (0.07-21.4)	0.90	1.03 (0.05-20.7)	0.98	1.47 (0.08-27.0)	0.79	1.78 (0.09-35.2)	0.70	1.22 (0.07-22.60)	0.90	1.84 (0.10-35.6)	0.69
Gender														
Male	0.91 (0.53-1.59)	0.75	0.89 (0.45-1.77)	0.75	0.84 (0.19-3.77)	0.82	1.39 (0.63-3.06)	0.41	0.41 (0.15-1.08)	0.069	0.78 (0.28-2.21)	0.65	0.94 (0.45-1.96)	0.87
Female	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Age at diagnosis	0.95 (0.92-0.98)	0.0010	0.96 (0.92-1.00)	0.045	1.07 (0.95-1.19)	0.26	0.95 (0.91-0.98)	0.0040	0.93 (0.87-0.98)	0.011	0.96 (0.91-1.01)	0.081	0.95 (0.92-0.99)	0.015
Preoperative KPS	1.96 (0.10-37.8)	0.66	1.71 (0.09-32.3)	0.72	2.22 (0.09-53.6)	0.62	2.49 (0.12-53.3)	0.56	1.66 (0.08-33.1)	0.74	NA		NA	
90-100	0.51 (0.03-9.83)	0.66	0.59 (0.03-11.0)	0.72	0.45 (0.02-10.8)	0.62	0.40 (0.02-8.59)	0.56	0.60 (0.03-12.0)	0.74	NA		NA	
≤ 80														

eTable 6: Factors independently predicting receival of adjuvant chemoradiotherapy (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative ASA score														
I	2.58 (0.42-16.0)	0.31	2.56 (0.38-17.4)	0.34	5.64 (0.17-181)	0.33	2.64 (0.23-30.9)	0.44	2.57 (0.26-25.6)	0.42	1.33 (0.13-13.3)	0.81	8.01 (0.81-79.1)	0.074
II	0.63 (0.13-3.18)	0.58	0.76 (0.14-4.30)	0.76	0.53 (0.03-8.28)	0.65	0.37 (0.04-3.13)	0.36	1.62 (0.24-11.1)	0.62	0.60 (0.07-4.95)	0.64	0.96 (0.15-6.26)	0.97
III	0.36 (0.07-1.78)	0.21	0.65 (0.11-3.68)	0.62	0.39 (0.02-6.89)	0.52	0.29 (0.03-2.47)	0.25	0.51 (0.08-3.34)	0.48	0.32 (0.04-2.77)	0.30	0.46 (0.07-2.88)	0.40
IV	NA		NA		NA		NA		NA		NA		NA	
Preoperative NIHSS score														
0-1	1.01 (0.06-17.5)	1.00	1.15 (0.07-20.5)	0.92	1.25 (0.06-26.8)	0.89	NA	1.00	NA		1.42 (0.07-27.5)	0.82	0.94 (0.05-16.7)	0.97
≥ 2	0.99 (0.06-17.3)	1.00	0.87 (0.05-15.4)	0.92	0.80 (0.04-17.2)	0.89	NA	1.00	NA		0.71 (0.04-13.7)	0.82	1.06 (0.06-18.7)	0.97
Tumor location by lobe														
Frontal	0.96 (0.17-5.39)	0.97	0.87 (0.05-15.4)	0.89	0.51 (0.04-7.21)	0.61	0.65 (0.09-4.57)	0.66	1.17 (0.16-8.64)	0.88	0.48 (0.05-4.55)	0.52	1.16 (0.20-6.76)	0.87
Parietal	1.00 (0.18-5.74)	1.00	1.29 (0.19-8.75)	0.79	5.96 (0.19-187)	0.31	0.80 (0.11-5.85)	0.83	1.23 (0.17-9.04)	0.84	0.76 (0.08-7.05)	0.81	0.81 (0.13-5.06)	0.82
Temporal	1.51 (0.27-8.59)	0.64	1.25 (0.19-8.27)	0.82	0.41 (0.03-6.07)	0.52	1.44 (0.20-10.4)	0.72	0.89 (0.12-6.45)	0.91	1.07 (0.11-9.97)	0.95	1.27 (0.21-7.67)	0.80
Occipital	1.32 (0.20-8.75)	0.77	1.25 (0.14-10.9)	0.84	1.45 (0.03-73.3)	0.85	0.84 (0.07-9.86)	0.89	1.21 (0.14-10.1)	0.86	3.60 (0.12-105)	0.46	0.80 (0.11-5.77)	0.82
Insula	NA		NA		NA		NA		NA		NA		NA	

eTable 6: Factors independently predicting receival of adjuvant chemoradiotherapy (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Tumor location by hemisphere														
Left	1.45 (0.76-2.79)	0.26	1.35 (0.59-3.10)	0.48	0.33 (0.04-2.54)	0.28	1.63 (0.63-4.24)	0.32	1.54 (0.57-4.14)	0.39	0.57 (0.17-1.93)	0.36	2.11 (0.92-4.88)	0.078
Right	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Tumor location by eloquence														
Motor	1.56 (0.62-3.91)	0.35	1.28 (0.42-3.96)	0.66	1.03 (0.13-8.40)	0.98	0.85 (0.18-4.07)	0.84	1.21 (0.38-3.87)	0.74	1.40 (0.25-8.00)	0.70	1.29 (0.44-3.76)	0.64
Sensory	4.59 (0.22-93.8)	0.32	2.45 (0.09-65.6)	0.59	1.03 (0.01-116)	0.99	2.28 (0.08-62.9)	0.63	2.95 (0.09-93.2)	0.54	3.82 (0.12-126)	0.45	2.76 (0.10-75.3)	0.55
Language	1.22 (0.41-3.63)	0.72	0.93 (0.25-3.43)	0.91	0.63 (0.06-7.08)	0.71	0.48 (0.08-2.83)	0.42	2.33 (0.49-11.1)	0.28	0.47 (0.07-3.11)	0.43	1.33 (0.37-4.77)	0.66
Visual	1.95 (0.87-4.37)	0.11	1.78 (0.65-4.88)	0.26	2.10 (0.24-18.7)	0.50	1.99 (0.58-6.81)	0.27	2.02 (0.62-6.61)	0.24	4.80 (0.84-27.6)	0.078	1.48 (0.55-3.97)	0.44
IDH status														
Wildtype	0.21 (0.02-1.45)	0.33	3.46 (0.18-67.5)	0.41	1.75 (0.05-60.6)	0.75	3.98 (0.21-74.4)	0.35	1.39 (0.03-70.1)	0.87	2.48 (0.11-57.7)	0.57	1.78 (0.05-59.3)	0.75
Mutant	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
MGMT status														
Methylated	1.06 (0.51-2.23)	0.87	1.73 (0.65-4.61)	0.27	0.53 (0.17-1.70)	0.28	1.44 (0.54-3.83)	0.46	0.71 (0.24-2.16)	0.55	0.60 (0.14-2.60)	0.50	1.12 (0.46-2.69)	0.81
Unmethylated	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Awake craniotomy	0.70 (0.28-1.73)	0.44	0.80 (0.29-2.18)	0.66	0.30 (0.05-1.77)	0.18	0.63 (0.21-1.92)	0.42	2.55 (1.29-22.4)	0.003	0.38 (0.10-1.38)	0.14	2.38 (1.20-10.6)	0.26

eTable 6: Factors independently predicting receival of adjuvant chemoradiotherapy (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	Overall [n= 1047]		<70 [n=625]		≥ 70 [n=422]		NIHSS 0-1 [n=621]		NIHSS ≥ 2 [n=426]		KPS 90-100 [n=492]		KPS ≤ 80 [n=555]	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Intraoperative ultrasound	0.71 (0.35-1.43)	0.33	0.78 (0.33-1.84)	0.57	0.83 (0.14-5.01)	0.83	0.58 (0.22-1.53)	0.27	0.71 (0.21-2.33)	0.57	1.33 (0.25-6.97)	0.73	0.62 (0.27-1.44)	0.27
Intraoperative fluorescence	0.65 (0.25-1.71)	0.38	0.37 (0.12-1.15)	0.085	0.17 (0.02-1.57)	0.12	0.53 (0.17-1.67)	0.28	1.26 (0.20-8.11)	0.81	0.37 (0.07-1.91)	0.24	1.11 (0.32-3.88)	0.87
6-week NIHSS, pre-op as ref														
Deteriorated	1.08 (0.58-2.01)	0.81	0.65 (0.30-1.40)	0.27	0.43 (0.08-2.18)	0.30	1.49 (0.67-3.31)	0.33	0.59 (0.20-1.70)	0.32	1.00 (0.34-2.94)	1.00	0.91 (0.40-2.08)	0.82
6-week KPS, pre-op as ref Deteriorated	0.18 (0.10-0.34)	0.0010	0.25 (0.12-0.52)	<0.0001	0.27 (0.06-1.30)	0.10	0.14 (0.06-0.32)	<0.0001	0.26 (0.10-0.69)	<0.0001	0.39 (0.13-1.20)	0.10	0.14 (0.07-0.30)	<0.0001
Postoperative vascular complications														
None	4.73 (0.49-45.8)	0.18	2.36 (0.21-27.2)	0.49	1.49 (0.09-25.5)	0.78	3.00 (0.24-37.2)	0.39	3.36 (0.26-42.6)	0.35	2.02 (0.10-42.8)	0.65	4.05 (0.32-51.1)	0.28
Major ischemia	1.32 (0.14-12.7)	0.81	1.14 (0.09-13.8)	0.93	0.35 (0.01-8.98)	0.52	0.91 (0.07-12.3)	0.94	1.60 (0.12-20.7)	0.72	2.19 (0.06-77.7)	0.67	0.78 (0.06-10.2)	0.85
Postop bleeding	0.52 (0.05-5.14)	0.58	0.35 (0.03-4.64)	0.43	1.68 (0.07-37.9)	0.74	0.37 (0.03-5.34)	0.47	0.31 (0.02-4.68)	0.40	0.19 (0.01-5.14)	0.33	0.36 (0.02-5.38)	0.46

eTable 6: Factors independently predicting receival of adjuvant chemoradiotherapy (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	Overall [n= 1047]		<70 [n=625]		≥ 70 [n=422]		NIHSS 0-1 [n=621]		NIHSS ≥ 2 [n=426]		KPS 90-100 [n=492]		KPS ≤ 80 [n=555]	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative CE tumor volume														
0-10 ml	1.04 (0.16-6.62)	0.97	1.44 (0.19-11.1)	0.73	0.36 (0.02-7.01)	0.50	0.65 (0.09-4.66)	0.67	3.48 (0.29-42.3)	0.33	0.97 (0.12-7.79)	0.98	0.78 (0.10-6.12)	0.81
10-25 ml	1.25 (0.22-7.21)	0.80	1.66 (0.26-10.5)	0.59	1.37 (0.13-14.8)	0.80	0.84 (0.14-5.19)	0.85	2.85 (0.29-42.3)	0.33	0.92 (0.14-6.17)	0.93	2.06 (0.30-14.0)	0.46
25-50 ml	1.19 (0.21-6.72)	0.84	0.97 (0.16-5.76)	0.97	1.82 (0.16-20.5)	0.63	1.22 (0.20-7.42)	0.83	0.88 (0.12-6.50)	0.90	1.66 (0.23-11.9)	0.62	1.11 (0.18-6.79)	0.91
50-100 ml	0.79 (0.14-4.49)	0.80	0.68 (0.11-4.10)	0.68	0.38 (0.04-3.62)	0.40	0.99 (0.21-11.1)	0.99	0.33 (0.04-3.54)	0.29	1.01 (0.13-7.61)	0.99	0.60 (0.10-3.68)	0.58
>100 ml	0.81 (0.13-4.96)	0.82	0.64 (0.10-4.14)	0.64	2.66 (0.17-40.4)	0.48	1.72 (0.17-17.5)	0.68	0.41 (0.05-3.48)	0.41	0.66 (0.06-6.99)	0.73	0.97 (0.14-6.49)	0.97
Postoperative CE tumor volume														
0-0.2 ml	1.00 (0.12-8.27)	1.00	0.65 (0.07-6.29)	0.71	1.44 (0.09-21.9)	0.79	1.72 (0.17-17.5)	0.65	0.74 (0.06-8.93)	0.81	1.04 (0.09-12.0)	0.98	1.18 (0.13-11.1)	0.89
0.2-1.0 ml	0.40 (0.05-2.99)	0.37	0.43 (0.05-3.58)	0.44	0.35 (0.03-4.49)	0.42	0.55 (0.07-4.54)	0.58	0.14 (0.01-1.53)	0.11	0.46 (0.05-4.11)	0.48	0.36 (0.04-3.02)	0.35
1.0-2.0 ml	1.34 (0.17-10.5)	0.78	1.22 (0.14-10.4)	0.86	1.30 (0.09-18.9)	0.85	0.92 (0.10-8.19)	0.94	1.66 (0.15-18.0)	0.67	1.01 (0.09-11.5)	0.99	1.14 (0.13-9.65)	0.91
>2.0 ml	1.76 (0.22-14.2)	0.59	3.23 (0.35-29.9)	0.30	1.40 (0.09-21.4)	0.81	1.16 (0.13-10.2)	0.90	4.23 (0.33-53.6)	0.26	2.12 (0.19-23.4)	0.54	1.91 (0.21-17.4)	0.56

eTable 6: Factors independently predicting receival of adjuvant chemoradiotherapy (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Extent of resection CE tumor														
98-100 %	2.51 (0.36-17.6)	0.35	5.20 (0.61-44.1)	0.13	1.51 (0.12-19.3)	0.75	1.03 (0.13-8.40)	0.98	13.2 (1.13-170)	0.012	2.57 (0.26-25.3)	0.42	2.39 (0.29-19.6)	0.41
95-98 %	0.77 (0.12-4.74)	0.78	0.96 (0.14-6.56)	0.97	0.76 (0.07-8.69)	0.83	0.89 (0.136.00)	0.90	0.38 (0.04-3.44)	0.39	1.09 (0.12-10.0)	0.94	0.65 (0.10-4.36)	0.66
90-95 %	1.49 (0.25-9.08)	0.66	1.46 (0.21-10.0)	0.70	1.21 (0.12-12.0)	0.87	1.49 (0.22-9.90)	0.68	1.98 (0.24-16.1)	0.52	1.52 (0.17-13.6)	0.71	1.65 (0.26-10.7)	0.60
80-90 %	0.71 (0.12-4.36)	0.71	0.43 (0.06-2.96)	0.39	0.46 (0.04-5.28)	0.53	1.40 (0.20-9.69)	0.73	0.40 (0.05-3.25)	0.39	0.83 (0.09-7.89)	0.87	0.56 (0.08-3.72)	0.55
<80 %	0.53 (0.09-3.22)	0.49	0.45 (0.07-3.03)	0.41	1.50 (0.14-16.2)	0.74	0.51 (0.08-3.35)	0.48	0.75 (0.09-5.94)	0.78	0.22 (0.03-2.01)	0.18	0.75 (0.12-4.84)	0.76
Interaction														
Awake*age	1.03 (0.66-1.64)	0.21	1.05 (0.25-1.36)	0.10	0.98 (0.23-1.70)	0.63	1.01 (0.44-1.29)	0.71	1.24 (0.51-1.52)	0.63	1.55 (0.29-1.22)	0.85	1.21 (0.07-1.60)	0.92
Awake*NIHSS	0.42 (0.33-1.43)	0.41	1.25 (0.77-1.46)	0.40	1.12 (0.25-1.17)	0.93	1.00 (0.97-1.03)	1.00	0.55 (0.12-1.99)	0.82	0.78 (0.30-1.82)	0.91	1.23 (0.75-1.45)	0.79
Awake*KPS	0.19 (0.12-1.08)	0.065	0.33 (0.11-1.95)	0.25	0.35 (0.12-1.44)	0.45	0.20 (0.11-1.54)	0.12	0.97 (0.64-1.33)	0.66	0.48 (0.60-1.27)	0.88	0.89 (0.76-1.40)	0.81

eTable 7: Factors independently predicting GTR on 0.0-0.2 ml residual CE tumor volume (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Center														
Rotterdam	0.24 (0.03-1.74)	0.26	0.20 (0.02-1.59)	0.13	0.88 (0.05-14.8)	0.93	0.25 (0.03-2.07)	0.20	0.14 (0.01-1.84)	0.13	0.30 (0.00-1.30)	0.12	0.17 (0.02-1.84)	0.14
The Hague	0.99 (0.137.35)	0.99	1.06 (0.13-8.53)	0.96	0.15 (0.01-3.49)	0.21	1.09 (0.13-9.04)	0.94	0.98 (0.07-13.1)	0.99	1.00 (0.01-145)	1.00	1.33 (0.11-16.6)	0.82
Leuven	2.73 (0.33-22.3)	0.35	1.91 (0.20-18.7)	0.58	5.86 (0.08-441)	0.40	1.02 (0.10-10.8)	0.98	4.30 (0.20-93.5)	0.34	2.22 (0.08-63.3)	0.81	2.22 (0.11-46.5)	0.60
Boston	1.30 (0.17-9.71)	0.80	1.77 (0.21-15.1)	0.60	1.44 (0.07-29.8)	0.80	2.30 (0.36-30.4)	0.29	2.3 (0.09-18.4)	0.84	2.19 (0.07-66.6)	0.48	1.39 (0.11-18.3)	0.80
Year of surgery														
2010-2015	0.79 (0.05-13.8)	0.87	0.93 (0.05-16.3)	0.96	0.82 (0.03-25.9)	0.90	0.71 (0.04-12.7)	0.81	0.59 (0.03-12.5)	0.73	1.09 (0.01-112)	0.97	0.47 (0.02-10.3)	0.63
2016-2020	1.26 (0.07-22.0)	0.87	1.07 (0.06-18.7)	0.96	1.22 (0.04-38.7)	0.90	1.41 (0.08-25.5)	0.81	1.69 (0.08-35.8)	0.73	0.92 (0.01-94.2)	0.97	2.12 (0.10-46.1)	0.63
Gender														
Male	0.93 (0.65-1.32)	0.68	0.82 (0.47-1.43)	0.49	1.32 (0.27-6.48)	0.72	0.72 (0.40-1.29)	0.27	0.86 (0.26-2.83)	0.80	0.49 (0.12-2.00)	0.30	1.63 (0.55-4.85)	0.37
Female	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Age at diagnosis	1.00 (0.98-1.01)	0.72	0.99 (0.96-1.01)	0.31	1.06 (0.87-1.30)	0.52	0.99 (0.97-1.02)	0.53	0.96 (0.91-1.02)	0.20	0.97 (0.91-1.03)	0.63	0.97 (0.92-1.02)	0.28
Preoperative KPS														
90-100	1.06 (0.06-18.2)	0.97	1.08 (0.06-18.9)	0.96	0.99 (0.04-25.4)	1.00	0.94 (0.05-16.6)	0.97	1.36 (0.07-27.4)	0.84	NA		NA	
≤ 80	0.94 (0.05-16.2)	0.97	0.93 (0.05-16.3)	0.96	1.01 (0.04-25.9)	1.00	1.06 (0.06-18.7)	0.97	0.73 (0.04-14.7)	0.84	NA		NA	

eTable 7: Factors independently predicting GTR on 0.0-0.2 ml residual CE tumor volume (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	Overall [n= 1047]		<70 [n=625]		≥ 70 [n=422]		NIHSS 0-1 [n=621]		NIHSS ≥ 2 [n=426]		KPS 90-100 [n=492]		KPS ≤ 80 [n=555]	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative ASA score														
I	0.65 (0.24-1.77)	0.40	1.40 (0.35-5.66)	0.63	1.31 (0.07-25.9)	0.85	0.90 (0.05-16.4)	0.90	1.21 (0.10-14.1)	0.88	0.43 (0.04-4.72)	0.27	2.56 (0.28-23.9)	0.40
II	0.57 (0.24-1.37)	0.21	0.86 (0.24-3.09)	0.82	3.59 (0.28-46.0)	0.30	0.76 (0.17-3.50	0.73	0.65 (0.08-5.61)	0.69	0.36 (0.04-3.32)	0.29	1.81 (0.27-12.3)	0.54
III	0.65 (0.28-1.53)	0.32	2.10 (0.59-7.49)	0.25	0.33 (0.02-5.32)	0.41	1.04 (0.23-4.77)	0.96	1.22 (0.16-9.32)	0.85	0.18 (0.01-2.23)	0.24	2.45 (0.44-13.5)	0.30
IV	NA		NA		NA		NA		NA		NA		NA	
Preoperative NIHSS score														
0-1	1.05 (0.06-18.1)	0.97	1.07 (0.06-18.8)	0.97	8.64 (0.12-627)	0.30	NA		NA		0.56 (0.03-12.4)	0.62	1.29 (0.07-25.0)	0.86
≥ 2	0.95 (0.06-16.3)	0.97	0.94 (0.05-16.5)	0.97	0.12 (0.00-8.41)	0.30	NA		NA		1.78 (0.08-39.4)	0.62	0.77 (0.04-15.0)	0.86
Tumor location by lobe														
Frontal	2.17 (0.46-10.2)	0.33	0.79 (0.11-5.71)	0.82	3.15 (0.17-57.9)	0.42	0.79 (0.11-5.93)	0.82	2.07 (0.22-19.5)	0.52	1.04 (0.10-10.5)	0.92	1.12 (0.12-10.1)	0.92
Parietal	2.01 (0.43-9.51)	0.38	0.85 (0.12-6.10)	0.87	1.48 (0.10-21.1)	0.76	0.71 (0.10-5.32)	0.74	0.83 (0.09-7.97)	0.87	0.84 (0.08-8.40)	0.82	2.52 (0.26-24.2)	0.42
Temporal	1.67 (0.35-7.87)	0.52	0.67 (0.09-4.79)	0.69	0.30 (0.02-5.14)	0.38	0.61 (0.08-4.55)	0.63	0.39 (0.04-3.89)	0.41	0.48 (0.05-5.01)	0.96	0.76 (0.08-7.1)	0.81
Occipital	4.65 (0.91-23.8)	0.065	2.47 (0.29-21.4)	0.41	0.67 (1.35-97.0)	0.81	3.71 (0.40-34.5)	0.25	1.45 (0.12-17.6)	0.77	2.61 (0.20-34.8)	0.87	0.45 (0.03-7.3)	0.57
Insula	NA		NA		NA		NA		NA		NA		NA	

eTable 7: Factors independently predicting GTR on 0.0-0.2 ml residual CE tumor volume (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	Overall [n= 1047]		<70 [n=625]		≥ 70 [n=422]		NIHSS 0-1 [n=621]		NIHSS ≥ 2 [n=426]		KPS 90-100 [n=492]		KPS ≤ 80 [n=555]	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Tumor location by hemisphere														
Left	1.13 (0.77-1.66)	0.52	0.70 (0.36-1.35)	0.29	1.46 (1.35-2.01)	0.018	0.97 (0.49-1.89)	0.92	0.62 (0.12-3.28)	0.56	1.44 (0.30-6.97)	0.84	0.74 (0.17-3.16)	0.68
Right	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Tumor location by eloquence														
Motor	0.79 (0.49-1.27)	0.33	1.33 (0.62-2.84)	0.46	0.04 (0.00-0.70)	0.020	1.16 (0.49-2.78)	0.73	0.47 (0.10-2.16)	0.32	0.52 (0.11-2.51)	0.68	0.07 (0.01-0.44)	0.004
Sensory	0.94 (0.42-2.09)	0.88	0.56 (0.14-2.28)	0.42	0.83 (0.01-46.2)	0.92	0.67 (0.14-3.16)	0.61	0.31 (0.01-10.5)	0.50	0.21 (0.01-4.11)	0.43	0.68 (0.02-22.7)	0.83
Language	1.01 (0.59-1.74)	0.96	1.76 (0.74-4.20)	0.20	0.58 (0.05-6.15)	0.63	1.82 (0.69-4.80)	0.22	1.37 (0.25-7.66)	0.71	1.17 (0.17-8.26)	0.44	0.08 (0.01-0.58)	0.012
Visual	0.79 (0.49-1.27)	0.33	1.08 (0.51-2.30)	0.84	0.93 (0.09-10.1)	0.95	1.06 (0.47-2.37)	0.89	0.74 (0.16-3.51)	0.70	1.42 (0.31-6.49)	0.51	0.08 (0.01-0.58)	0.12
IDH status														
Wildtype	1.34 (0.49-3.83)	0.55	1.16 (0.28-4.72)	0.82	1.00 (0.01-158)	1.00	2.21 (0.62-12.2)	0.24	1.00 (0.01-168)	1.00	2.57 (0.76-14.1)	0.15	1.00 (0.01-154)	1.00
Mutant	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
MGMT status														
Methylated	0.65 (0.44-1.39)	0.28	0.76 (0.40-1.39)	0.37	0.89 (0.25-3.12)	0.85	0.80 (0.43-1.50)	0.48	1.17 (0.28-4.87)	0.82	0.65 (0.33-1.28)	0.21	1.36 (0.44-4.14)	0.58
Unmethylated	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Awake craniotomy	1.88 (1.14-3.10)	0.013	1.86 (1.08-3.43)	0.028	2.31 (1.27-20.1)	0.012	1.97 (1.04-3.73)	0.038	1.35 (0.35-5.19)	0.66	2.44 (1.44-13.5)	0.0080	2.19 (0.69-6.96)	0.18

eTable 7: Factors independently predicting GTR on 0.0-0.2 ml residual CE tumor volume (Multiple multivariable logistic regression, unmatched cohorts) (continued)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Intraoperative ultrasound	1.68 (1.04-2.72)	0.034	1.76 (0.79-3.93)	0.16	1.33 (0.09-19.5)	0.83	1.59 (0.67-3.75)	0.29	1.33 (0.25-7.00)	0.73	5.23 (0.52-52.3)	0.15	3.67 (0.93-14.4)	0.059
Intraoperative fluorescence	0.86 (0.36-2.06)	0.73	0.94 (0.23-3.92)	0.93	5.86 (0.08-442)	0.40	2.32 (0.48-11.5)	0.30	1.36 (0.02-5.61)	0.46	0.31 (0.02-5.51)	0.68	0.94 (0.06-14.6)	0.96
Preoperative CE tumor volume														
0-10 ml	1.88 (0.33-10.6)	0.47	1.66 (0.29-9.65)	0.57	0.21 (0.01-5.86)	0.33	2.59 (0.41-16.4)	0.31	1.36 (0.13-14.8)	0.80	15.6 (1.03-236.4)	0.22	5.24 (0.52-52.9)	0.16
10-25 ml	1.41 (0.26-7.75)	0.69	0.71 (0.13-3.75)	0.69	2.20 (0.18-26.5)	0.51	1.59 (0.27-9.35)	0.61	0.79 (0.09-6.93)	0.83	1.81 (0.19-17.1)	0.99	0.60 (0.07-4.95)	0.63
25-50 ml	0.91 (0.17-4.98)	0.92	0.37 (0.07-1.97)	0.24	1.81 (0.14-23.1)	0.63	0.64 (0.11-3.74)	0.62	2.29 (0.27-19.2)	0.44	1.09 (0.11-10.5)	0.58	2.00 (0.26-15.1)	0.50
50-100 ml	0.88 (0.16-4.80)	0.88	0.43 (0.08-2.31)	0.33	1.57 (0.11-21.5)	0.72	0.78 (0.13-4.58)	0.79	0.59 (0.06-5.68)	0.64	0.34 (0.03-4.07)	0.82	0.69 (0.09-5.32)	0.72
>100 ml	0.46 (0.08-2.57)	0.37	0.33 (0.06-1.95)	0.22	0.41 (0.01-18.9)	0.63	0.52 (0.08-3.30)	0.49	0.64 (0.01-33.1)	0.82	0.12 (0.00-7.53)	0.85	0.29 (0.02-3.56)	0.33
Interaction	1.00 (1.00-1.01)	0.77	1.02 (0.56-1.34)	0.69	1.24 (0.12-2.31)	0.78	1.42 (0.28-1.46)	0.74	0.87 (0.45-1.32)	0.74	0.85 (0.34-1.25)	0.82	0.53 (0.23-1.62)	0.73
Awake*age	0.66 (0.23-1.43)	0.50	0.89 (0.89-1.12)	0.72	0.86 (0.03-3.14)	0.36	1.21 (0.23-1.72)	0.73	0.96 (0.23-1.77)	0.93	0.82 (0.24-1.62)	0.52	0.73 (0.11-1.91)	0.96
Awake*NIHSS	0.58 (0.32-1.55)	0.47	1.12 (0.81-1.30)	0.85	1.24 (0.85-1.34)	0.62	0.73 (0.46-1.32)	0.85	1.08 (0.88-1.13)	0.79	1.12 (0.66-1.12)	0.66	0.84 (0.25-1.37)	0.64
Awake*KPS														

eTable 8: Factors independently predicting GTR based on 98-100% extent of resection (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Center														
Rotterdam	0.28 (0.04-2.03)	0.21	0.20 (0.02-1.80)	0.15	0.73 (0.04-12.7)	0.82	0.40 (0.05-3.48)	0.40	0.15 (0.01-2.22)	0.16	0.30 (0.00-1.11)	0.34	0.06 (0.00-1.08)	0.12
The Hague	0.77 (0.10-5.66)	0.79	0.44 (0.05-3.90)	0.46	0.18 (0.01-4.22)	0.26	1.10 (0.12-9.90)	0.93	0.41 (0.03-6.34)	0.52	1.00 (0.01-145)	1.00	0.56 (0.04-8.46)	0.65
Leuven	3.16 (0.39-25.4)	0.30	2.69 (0.25-28.7)	0.41	4.38 (0.07-544)	0.39	0.52 (0.04-6.32)	0.61	14.9 (0.50-445)	0.11	1.52 (0.05-45.0)	0.81	2.40 (0.09-63.2)	0.35
Boston	1.43 (0.19-10.6)	0.73	4.07 (0.40-41.9)	0.24	1.69 (0.07-42.5)	0.74	1.15 (0.82-1.44)	0.11	2.41 (0.15-40.1)	0.53	3.87 (0.09-173)	0.48	6.04 (0.32-115)	0.85
Year of surgery														
2010-2015	0.76 (0.04-13.2)	0.85	0.73 (0.04-13.0)	0.83	0.74 (0.02-27.0)	0.87	0.62 (0.03-11.4)	0.75	0.54 (0.03-11.6)	0.69	1.09 (0.01-112)	0.97	0.45 (0.02-9.83)	0.76
2016-2020	1.32 (0.08-23.1)	0.85	1.38 (0.08-24.6)	0.83	1.34 (0.04-48.2)	0.87	1.62 (0.09-29.8)	0.75	1.85 (0.09-40.0)	0.69	0.91 (0.01-93.6)	0.97	2.20 (0.10-47.8)	0.76
Gender														
Male	0.98 (0.71-1.36)	0.91	0.86 (0.51-1.46)	0.58	2.31 (0.37-14.4)	0.35	0.71 (0.40-1.24)	0.22	2.13 (0.66-6.93)	0.20	0.48 (0.12-1.98)	0.30	2.66 (0.96-7.40)	0.41
Female	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Age at diagnosis	0.99 (0.98-1.01)	0.28	0.98 (0.95-1.00)	0.10	1.07 (0.87-1.32)	0.51	0.98 (0.96-1.01)	0.21	0.95 (0.90-1.01)	0.10	0.98 (0.92-1.05)	0.63	0.96 (0.92-1.01)	0.57
Preoperative KPS														
90-100	1.08 (0.06-18.6)	0.96	1.09 (0.06-19.2)	0.95	0.74 (0.03-20.2)	0.85	1.04 (0.06-18.2)	0.98	1.10 (0.06-21.6)	0.95	NA		NA	
≤ 80	0.92 (0.05-15.8)	0.96	0.91 (0.05-16.0)	0.95	1.35 (0.05-37.1)	0.85	0.97 (0.05-17.0)	0.98	0.91 (0.05-18.0)	0.95	NA		NA	

eTable 8: Factors independently predicting GTR based on 98-100% extent of resection (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Preoperative ASA score														
I	0.66 (0.25-1.78)	0.42	1.13 (0.26-4.92)	0.87	1.91 (0.08-45.1)	0.67	1.10 (0.18-661)	0.92	1.40 (0.11-17.4)	0.79	0.26 (0.02-3.00)	0.27	12.3 (0.99-153)	0.061
II	0.63 (0.26-1.53)	0.30	0.73 (0.18-2.98)	0.66	5.80 (0.43-77.7)	0.16	0.81 (0.14-4.62)	0.81	1.20 (0.14-9.80)	0.87	0.30 (0.03-2.90)	0.29	10.7 (1.17-97.5)	0.28
III	0.57 (0.24-1.36)	0.20	1.37 (0.33-5.66)	0.66	0.86 (0.06-12.2)	0.91	1.11 (0.19-6.41)	0.91	1.15 (0.14-9.80)	0.89	0.22 (0.02-2.78)	0.24	1.84 (0.28-12.3)	0.51
IV	NA		NA		NA		NA		NA		NA		NA	
Preoperative NIHSS score														
0-1	1.01 (0.06-17.4)	0.99	0.86 (0.05-15.1)	0.92	5.69 (0.11-302)	0.37	NA		NA		0.46 (0.02-10.6)	0.62	1.00 (0.05-18.8)	0.89
≥ 2	0.99 (0.06-16.9)	0.99	1.17 (0.07-20.6)	0.92	0.18 (0.00-9.33)	0.37	NA		NA		2.18 (0.09-50.7)	0.62	1.00 (0.05-18.9)	0.89
Tumor location by lobe														
Frontal	2.67 (0.59-12.1)	0.20	0.86 (0.12-6.22)	0.88	1.57 (0.08-30.9)	0.76	0.68 (0.09-5.11)	0.70	2.98 (0.30-29.4)	0.34	1.12 (0.12-10.8)	0.92	1.06 (0.12-9.00)	0.34
Parietal	2.39 (0.53-10.9)	0.26	0.69 (0.10-4.97)	0.71	3.58 (0.20-63.8)	0.36	0.67 (0.09-5.05)	0.70	0.68 (0.07-6.65)	0.74	0.76 (0.08-7.51)	0.82	1.44 (0.16-12.7)	0.52
Temporal	2.42 (0.53-11.0)	0.25	0.70 (0.10-5.01)	0.72	016 (0.01-3.37)	0.21	0.71 (0.09-5.28)	0.73	0.61 (0.06-6.07)	0.67	0.95 (0.10-9.05)	0.96	0.68 (0.08-5.90)	0.63
Occipital	5.41 (1.10-26.7)	0.038	2.75 (0.32-23.7)	0.36	0.77 (0.02-30.8)	0.89	4.56 (0.47-44.2)	0.19	0.91 (0.08-10.9)	0.94	1.25 (0.09-17.3)	0.87	0.96 (0.07-13.0)	0.70
Insula	NA		NA		NA		NA		NA		NA		NA	

eTable 8: Factors independently predicting GTR based on 98-100% extent of resection (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Tumor location by hemisphere														
Left	1.35 (0.94-1.93)	0.10	0.93 (0.50-1.75)	0.83	2.61 (1.80-2.59)	0.011	1.63 (0.84-3.13)	0.15	2.15 (0.44-10.5)	0.34	1.17 (0.26-5.27)	0.84	1.22 (0.30-4.94)	0.39
Right	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Tumor location by eloquence														
Motor	0.94 (0.60-1.46)	0.77	1.82 (0.89-3.71)	0.097	0.06 (0.00-1.21)	0.053	0.93 (0.40-2.13)	0.85	0.74 (0.15-3.75)	0.71	0.70 (0.13-3.90)	0.68	0.28 (0.05-1.44)	0.36
Sensory	1.08 (0.50-2.33)	0.85	0.70 (0.18-2.76)	0.61	3.67 (0.05-271)	0.53	0.84 (0.18-3.91)	0.82	1.38 (0.07-28.5)	0.83	0.31 (0.02-5.71)	0.43	0.24 (1.01-4.97)	0.28
Language	1.30 (0.78-2.17)	0.31	2.94 (1.27-6.83)	0.012	1.53 (0.09-25.4)	0.76	1.78 (0.70-4.53)	0.23	2.35 (0.36-15.2)	0.36	2.22 (0.29-17.1)	0.44	0.11-3.97) 0.91	0.54
Visual	1.02 (0.66-1.58)	0.93	1.38 (0.69-2.77)	0.36	0.37 (0.03-5.19)	0.43	0.96 (0.44-2.06)	0.91	1.00 (0.21-4.76)	1.00	1.67 (0.35-8.04)	0.51	(0.20-4.05)	0.42
IDH status														
Wildtype	0.92 (0.33-2.54)	0.88	0.72 (0.16-2.71)	0.61	1.00 (0.01-159)	1.00	1.56 (0.42-8.20)	0.51	1.00 (0.01-168)	1.00	1.31 (0.36-5.54)	0.67	1.00 (0.01-154)	1.00
Mutant	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
MGMT status														
Methylated	0.70 (0.48-1.02)	0.067	0.63 (0.33-1.13)	0.13	0.73 (0.20-2.69)	0.63	0.81 (0.43-1.51)	0.51	0.55 (0.13-2.24)	0.38	0.67 (0.33-1.29)	0.23	1.17 (0.38-3.63)	0.78
Unmethylated	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Awake craniotomy	2.14 (1.31-3.52)	0.003	1.39 (0.76-2.54)	0.28	7.61 (0.50-117)	0.12	2.01 (1.05-3.82)	0.033	0.64 (0.17-2.43)	0.50	1.48 (1.26-8.34)	0.029	1.86 (0.62-5.58)	0.26

eTable 8: Factors independently predicting GTR based on 98-100% extent of resection (Multiple multivariable logistic regression, unmatched cohorts)

Group	**Overall [n= 1047]**		**<70 [n=625]**		**≥ 70 [n=422]**		**NIHSS 0-1 [n=621]**		**NIHSS ≥ 2 [n=426]**		**KPS 90-100 [n=492]**		**KPS ≤ 80 [n=555]**	
Characteristic	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
Intraoperative ultrasound	1.62 (1.03-2.54)	0.036	0.98 (0.45-2.11)	0.95	2.09 (0.12-35.1)	0.59	1.34 (0.56-3.17)	0.51	0.94 (0.20-4.40)	0.94	4.88 (0.54-43.9)	0.15	2.30 (0.63-8.40)	0.20
Intraoperative fluorescence	1.26 (0.60-2.66)	0.54	0.81 (0.20-3.25)	0.76	6.38 (0.07-544)	0.39	7.42 (1.31-42.0)	0.023	0.34 (0.02-6.04)	0.45	0.57 (0.04-8.54)	0.68	1.69 (0.08-37.6)	0.74
Preoperative CE tumor volume														
0-10 ml	1.00 (0.18-5.48)	1.00	1.64 (0.29-9.27)	0.57	0.26 (0.01-7.15)	0.40	1.31 (0.21-8.02)	0.77	0.55 (0.05-5.82)	0.61	4.49 (0.39-51.9)	0.22	1.23 (0.13-11.5)	0.85
10-25 ml	1.28 (0.24-6.85)	0.77	1.22 (0.24-6.33)	0.81	1.19 (0.10-14.2)	0.88	1.31 (0.23-7.46)	0.76	0.53 (0.06-4.48)	0.56	0.99 (0.12-8.35)	0.99	0.59 (0.08-4.50)	0.60
25-50 ml	0.76 (0.14-4.02)	0.74	0.70 (0.14-3.58)	0.67	1.03 (0.08-13.3)	0.98	0.51 (0.09-2.90)	0.45	1.37 (0.17-10.9)	0.76	0.54 (0.06-4.89)	0.58	1.49 (0.22-10.2)	0.68
50-100 ml	0.99 (0.19-5.25)	0.99	1.15 (0.22-5.92)	0.86	1.89 (0.14-26.0)	0.62	0.88 (0.16-4.98)	0.88	1.66 (0.19-14.9)	0.64	0.76 (0.08-7.49)	0.82	0.79 (0.12-5.33)	0.80
>100 ml	1.04 (0.19-5.59)	0.96	1.21 (0.22-6.62)	0.83	1.24 (0.04-40.6)	0.90	1.26 (0.21-7.51)	0.80	1.53 (0.06-37.6)	0.79	0.71 (0.02-26.6)	0.85	1.17 (0.13-10.3)	0.88
Interaction														
Awake*age	1.01 (0.54-1.21)	0.89	1.23 (0.77-1.45)	0.86	0.89 (0.75-1.11)	0.96	0.77 (0.34-1.11)	0.91	1.23 (0.13-1.56)	0.87	1.52 (0.25-1.87)	0.89	1.07 (0.35-1.40)	0.66
Awake*NIHSS	2.60 (0.76-3.29)	0.12	1.41 (0.69-1.36)	0.78	0.95 (0.80-1.17)	0.83	1.52 (0.86-1.70)	0.24	1.05 (0.13-1.33)	0.48	1.24 (0.12-2.52)	0.94	0.56 (0.26-1.83)	0.25
Awake*KPS	0.94 (0.33-1.56)	0.40	1.28 (0.78-1.74)	0.66	1.11 (0.74-1.42)	0.70	1.32 (0.43-1.99)	0.51	0.98 (0.56-1.41)	0.80	0.77 (0.36-2.25)	0.72	0.82 (0.25-1.44)	0.81

eTable 9: Results of the propensity-score matching – standardized mean differences before and after matching of included covariates

	Overall		**<70**		**≥ 70**		**NIHSS 0-1**		**NIHSS ≥ 2**		**KPS 90-100**		**KPS ≤ 80**	
Group	**Un-matched [n= 1047]**	**Matched [n= 536]**	**Un-matched [n=625]**	**Matched [n=456]**	**Un-matched [n=422]**	**Matched [n=80]**	**Un-matched [n=621]**	**Matched [n=428]**	**Un-matched [n=426]**	**Matched [n=108]**	**Un-matched [n=492]**	**Matched [n=396]**	**Un-matched [n=555]**	**Matched [n=140]**
Variable	SMD	SMD	SMD	SMD	SMD	SMD	SMD	SMD	SMD	SMD	SMD	SMD	SMD	SMD
Gender	-0.14	-0.03	-0.13	-0.04	-0.03	-0.03	-0.10	-0.04	-0.13	-0.10	-0.03	-0.09	0.10	0.08
Age	-0.27	-0.30	-0.32	0.23	-0.15	-0.04	-0.20	-0.32	-0.32	-0.04	-0.15	-0.30	-0.29	-0.02
Preoperative KPS	0.82	0.20	0.72	0.34	1.06	-0.11	0.66	0.25	0.72	0.04	1.06	0.20	0.47	0.24
Preoperative NIHSS score	-0.58	-0.17	-0.50	-0.21	-0.92	-0.30	-0.21	-0.09	-0.50	-0.01	-0.91	-0.22	-0.23	-0.08
Preoperative tumor volume	-0.48	-0.23	-0.54	-0.27	-0.58	-0.27	-0.34	-0.26	-0.54	-0.04	-0.58	-0.26	-0.58	-0.13
Tumor location by lobe	-0.19	-0.10	-0.24	-0.18	0.06	0.04	-0.26	-0.20	-0.24	-0.07	0.06	-0.20	-0.15	-0.20
Tumor location by hemisphere	-0.73	-0.19	-0.80	-0.32	-0.40	-0.04	-0.54	-0.25	-0.80	-0.31	-0.40	-0.04	-0.86	0.08
Intraoperative fluorescence	0.18	0.08	0.13	0.07	0.14	-0.09	0.21	0.16	0.13	0.16	0.14	0.06	0.11	0.03
Year of surgery	-0.39	-0.02	-0.48	0.02	0.12	-0.11	-0.42	-0.05	-0.48	0.02	0.12	0.06	-0.74	-0.04
Center	0.33	0.45	0.54	0.44	0.40	0.59	0.48	0.56	0.55	0.19	0.40	0.50	0.31	0.37
Adjuvant chemotherapy and radiotherapy	0.44	0.12	0.30	0.14	0.53	0.30	0.40	0.22	0.30	0.01	0.53	0.03	0.79	0.07

Standardized mean differences (SMDs) for covariates before and after matching for the overall cohort and subgroups.
Abbreviations: KPS: Karnofsky Performance Score; NIHSS: National Institute of Health Stroke Scale.

eTable 10: Etiology analysis for awake craniotomy and surgical outcomes (Multiple multivariable Cox proportional-hazards regression, matched cohorts)

Group	Overall [n= 536]		<70 [n=456]		≥ 70 [n=80]		NIHSS 0-1 [n=428]		NIHSS ≥ 2[n=108]		KPS90-100 [n=396]		KPS≤ 80 [n=140]	
Characteristic	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*
NIHSS deterioration	1.02 (0.76-1.38)	0.87	1.01 (0.72-1.43)	0.94	0.89 (0.44-1.77)	0.73	1.05 (0.75-1.47)	0.78	0.57 (0.23-1.42)	0.23	0.89 (0.62-1.62)	0.50	1.16 (0.54-2.28)	0.71
KPS deterioration	1.08 (0.78-1.50)	0.63	1.14 (0.80-1.61)	0.47	0.94 (0.48-1.83)	0.85	1.07 (0.77-1.50)	0.69	1.03 (0.44-2.42)	0.95	1.13 (0.80-1.60)	0.49	0.96 (0.45-2.06)	0.92
Adjuvant therapy	1.02 (0.75-1.39)	0.90	0.98 (0.69-1.39)	0.89	1.09 (0.56-2.15)	0.79	1.09 (0.67-1.28)	0.73	0.97 (0.43-2.21)	0.95	0.98 (0.70-1.39)	0.92	0.94 (0.48-1.86)	0.87
Gross-total resection based on RTV of CE tumor	1.49 (1.09-1.88)	0.013	1.41 (0.98-1.49)	0.065	1.59 (0.31-1.91)	0.20	1.35 (0.52-1.50)	0.079	1.89 (0.21-1.34)	0.18	1.45 (1.02-1.48)	0.045	0.78 (0.39-1.55)	0.47
Gross-total resection based on EOR of CE tumor	1.39 (1.05-1.65)	0.038	1.33 (0.52-1.78)	0.12	1.64 (0.30-1.22)	0.16	1.37 (0.52-1.89)	0.075	1.20 (0.35-2.00)	0.69	1.52 (1.05-1.46)	0.026	0.97 (0.49-1.92)	0.94
Overall survival	0.63 (0.40-0.99)	0.048	0.67 (0.39-1.14)	0.14	0.57 (0.21-1.53)	0.27	0.79 (0.49-1.27)	0.47	0.46 (0.13-1.60)	0.22	0.79 (0.47-1.34)	0.38	0.41 (0.14-1.5)	0.090
Progression-free survival	0.85 (0.63-1.15)	0.30	0.80 (0.57-1.12)	0.19	0.82 (0.42-1.59)	0.55	0.95 (0.69-1.33)	0.78	0.83 (0.36-1.91)	0.67	1.00 (0.71-1.41)	0.98	0.60 (0.31-1.20)	0.15

Analysis of the time-dependent etiological effect of the main exposure of the propensity score matching (awake craniotomy) on surgical outcomes adjusted for *IDH* mutation status and MGMT methylation status.

Abbreviations: KPS: Karnofsky Performance Score; NIHSS: National Institute of Health Stroke Scale; RTV: Residual Tumor Volume; CE: contrast-enhancing; EOR: Extent of Resection; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase.

eTab le 11: Sensitivity analysis based on matched covariates with SMD > 0.20 (Multiple multivariable Cox proportional-hazards regression, matched cohorts)

Group	Overall [n= 536]		<70 [n=456]		≥ 70 [n=80]		NIHSS 0-1 [n=428]		NIHSS ≥ 2 [n=108]		KPS 90-100 [n=396]		KPS ≤ 80 [n=140]	
Characteristic	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*	**HR (95% CI)**	*p*
NIHSS deterioration	0.88 (0.62-1.23)	0.45	0.80 (0.53-1.22)	0.31	0.89 (0.32-2.44)	0.82	0.75 (0.50-1.12)	0.16	0.99 (0.25-3.92)	0.99	1.26 (0.85-1.88)	0.25	1.17 (0.51-2.64)	0.71
KPS deterioration	1.13 (0.80-1.58)	0.49	1.18 (0.77-1.79)	0.45	1.02 (0.56-4.17)	0.80	1.15 (0.78-1.71)	0.47	1.60 (0.38-6.70)	0.52	1.22 (0.84-1.79)	0.30	1.04 (0.68-3.11)	0.93
Adjuvant therapy	1.05 (0.75-1.46)	0.79	1.03 (0.69-1.53)	0.89	1.02 (0.35-2.94)	0.97	1.10 (0.75-1.61)	0.63	1.18 (0.37-3.74)	0.78	1.10 (0.75-1.61)	0.64	1.00 (0.48-2.09)	1.00
Gross-total resection based on RTV of CE tumor	1.37 (1.03-1.92)	0.042	1.19 (0.81-1.72)	0.37	0.64 (0.11-1.35)	0.22	1.02 (0.70-1.49)	0.92	1.49 (0.56-6.25)	0.43	1.54 (1.03-2.27)	0.035	0.65 (0.28-1.52)	0.32
Gross-total resection based on EOR of CE tumor	1.30 (0.93-1.82)	0.14	1.22 (0.84-1.79)	0.29	1.89 (0.83-4.35)	0.13	0.94 (0.64-1.38)	0.74	0.92 (0.36-2.34)	0.86	1.56 (1.04-2.33)	0.030	0.94 (0.43-2.07)	0.88
Overall survival	0.92 (0.53-1.58)	0.76	0.99 (0.58-1.69)	0.97	0.52 (0.21-1.30)	0.16	0.70 (0.39-1.25)	0.22	0.11 (0.01-1.20)	0.070	0.79 (0.44-1.44)	0.45	0.66 (0.17-2.64)	0.56
Progression-free survival	0.90 (0.63-1.28)	0.57	0.91 (0.63-1.31)	0.62	0.41 (0.18-0.95)	0.038	0.84 (0.58-1.21)	0.34	0.63 (0.22-1.79)	0.38	0.98 (0.69-1.39)	0.91	0.97 (0.64-1.48)	0.49

Sensitivity analysis of the etiological analysis model adjusted for *IDH* mutation status, MGMT methylation status and matched covariates with a standardized mean difference greater than 0.20 in one or multiple of the propensity-score matching procedures: center, age, hemisphere, preoperative tumor volume, adjuvant therapy, preoperative NIHSS score, and preoperative KPS score.
Abbreviations: SMD: Standardized Mean Difference; KPS: Karnofsky Performance Score; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast-enhancing.

CHAPTER 11

Impact of maximal extent of resection on postoperative deficits, patient functioning and survival within clinically important glioblastoma subgroups

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ABSTRACT

Background

Maximizing extent of resection is one of the main goals in glioblastoma surgery. The impact of extent of resection and residual tumor volume in patient subgroups is currently unknown. Furthermore, it has not been studied before in correlation with neurological and functional outcomes. This study aimed to analyze its impact in subgroups of patients with eloquent glioblastoma with incorporation of neurological and functional outcomes.

Methods

The presented study is a supplementary analysis of the international multicenter GLIOMAP study which included 918 patients from four tertiary care centers in the Netherlands, Belgium and the United States with eloquent glioblastomas. We analyzed the impact of extent of resection, residual tumor volume and gross-total resection on postoperative neurological deficits, postoperative KPS deterioration, receipt of adjuvant chemoradiotherapy, overall survival (OS) and progression-free survival (PFS).

Results

Multivariate Cox regression analyses showed that an extent of resection of 98-100% significantly decreased the overall risk of neurological (NIHSS) deterioration at 6 weeks postoperatively (OR 0.55, 95% CI 0.33-0.93, p = 0.026). Gross-total resection (GTR) based on extent of resection (98-100%) or residual tumor volume (0.0-0.2 ml) was not significantly associated with postoperative KPS deterioration or receipt of adjuvant therapy. GTR based on residual volume was independently predictive for OS in the overall cohort (HR 0.44, 95% CI 0.23-0.85, p = 0.015), in patients aged ≥ 70 (HR 0.08, 95% CI 0.02-0.30, p = 0.004) and in patients with a preoperative NIHSS score of ≥ 2 (HR 0.07, 95% CI 0.01-0.40, p = 0.003), while GTR based on 98-100% EOR was only significantly predictive for OS in the KPS ≤ 80 subgroup (HR 0.11, 95% CI 0.09-0.49, p = 0.016). GTR based on EOR was significantly predictive for PFS in the KPS ≤ 80 subgroup (HR 0.19, 95% CI 0.06-0.65, p = 0.008). Kaplan-Meier analyses indicated that a higher extent of resection or lower residual tumor volume significantly improved OS and PFS for all subgroups except the NIHSS 0-1 subgroup for OS and the subgroups aged ≥ 70 and KPS 90-100 for PFS. The combined achievement of GTR and preservation of neurological function yielded the longest survival times (median OS 29.5 months [95% CI 20.0-41.0], p<0.0001).

Conclusions

A higher extent of resection and lower residual tumor volume were associated with improved OS and PFS outcomes. GTR was especially beneficial for OS improvement in the subgroups aged ≥ 70, NIHSS score ≥ 2 and KPS ≤ 80 without increasing the risk of postoperative

NIHSS or KPS worsening. These findings may assist surgical decision making in individual glioblastoma patients.

INTRODUCTION

Maximizing extent of resection (EOR) is often one of the main goals in glioblastoma surgery. Previous evidence strongly suggests that EOR is a strong predictor of overall survival in glioblastoma patients [1-5] including elderly patients [6-8]. Residual tumor volume has been introduced rather recently as a means to assess volumetric tumor reduction and has been indicated to be a better predictor of survival outcomes than EOR [9,10]. Moreover, it seems that gross-total resection (GTR) of the contrast-enhancing (CE) and non-contrast-enhancing (NCE) part of the tumor yields the best survival outcomes in glioblastoma patients [10], although there is currently no consensus on the exact volumetric or percent-based threshold for assessing GTR [11]. The current evidence forms a solid foundation but a few important questions remain to be addressed adequately.

First, the association of extent of resection and residual volume has been evaluated previously in glioblastoma patients in general [1-5], in elderly patients [6-8], and in molecular subgroups (*IDH* mutation status, MGMT methylation status) [10]. However, there is currently no data available regarding the impact of EOR, GTR and residual volume in clinically relevant patient subgroups based on for example preoperative neurological status or KPS which hampers objective assessment of surgical strategies. Second, studies have been focusing on the impact of these cytoreductive measures in glioblastoma patients with both eloquent and non-eloquent located tumors. Though, pursuing GTR in eloquent glioblastomas makes the patient often more susceptible to postoperative neurological deficits and functional worsening, which means that the surgeon has to balance between aggressive cytoreduction and surgical safety. This implies that tumor resection for eloquent glioblastoma differs significantly from the resection of non-eloquent tumors. Consequently, investigating the impact of EOR, GTR and residual tumor volume in eloquent glioblastomas specifically is much needed. Third, the impact of these measures should not be evaluated by survival outcomes alone but in conjunction with markers of surgical safety, for example neurological deficits and KPS to adequately address the surgical objectives. Indeed, in glioblastoma patients, cytoreduction can only be considered valuable when the patient has not deteriorated significantly postoperatively.

With due consideration of the aforementioned scientific hiatuses, we aimed to analyze the impact of extent of resection, residual tumor volume and gross-total resection on postoperative neurological deficits, postoperative KPS worsening, receipt of adjuvant therapy, overall survival and progression-free survival. All analyses were performed in subgroups of a multicenter cohort of primary, eloquently located glioblastoma patients based on age, preoperative neurological functioning and preoperative KPS. The results of this study will serve consequently as useful objective data for potential re-assessment of surgical strategies.

Figure 1: Data Flow Diagram

METHODS

The presented study is a supplementary analysis of the international multicenter GLIOMAP study, which was prospectively designed and retrospectively carried out in four tertiary neurosurgical care institutes in the Netherlands (Rotterdam, The Hague), Belgium (Leuven) and the United States (Boston). It was approved by the ethical committee of all centers and adhered to the STROBE reporting guidelines and concerned the screening of 4075 patients with glioblastoma surgery between January 2010 and October 2020 for eligibility (Figure 1). Cases that consisted of biopsies, tumors in non-eloquent areas (Sawaya grade I), multifocal tumors, midline tumors, recurrent or secondary tumors and patients with incomplete clinical data were excluded. Ultimately, 918 patients with a first tumor resection for eloquently located glioblastoma were included. Patient, tumor, clinical and imaging related data was collected for all eligible patients. The GLIOMAP study was designed to evaluate the impact of awake mapping in subgroups of glioblastoma patients. Therefore, patients in the awake mapping group were matched with patients in the asleep group for the overall cohort and for six subgroups that were based on age (<70 vs. ≥70), preoperative NIHSS score (0-1 vs. ≥2) and preoperative KPS (90-100 vs ≤80). The matched overall cohort and matched subgroups were then analyzed for the primary outcomes postoperative neurological deficits, postoperative KPS, extent of resection, residual tumor volume, receival of adjuvant therapy, overall survival and progression-free survival. Additional details on data collection can be found in the eMethods section (Data Supplement).

Statistical analysis

All analyses were performed using *R* (version 4.1.0, R Institute for Statistical Computing, Vienna, Austria) and are largely identical to the analyses performed for the GLIOMAP study. Demographic cohort data were summarized using standard descriptive statistics. The alpha for statistical significance was set at 5% for all tests. To test for differences in categorical variables, the Pearson's χ^2 test was used. For continuous variables with 2 variables, the two-tailed *t*-test for independent groups was used. For >2 groups, the one-way ANOVA test was performed. Patients in the awake craniotomy group were matched with a 1:3 ratio with patients from the asleep resection group (*matchit* package in *R*: nearest neighbor propensity score matching) based on the factors gender, age, preoperative KPS, preoperative NIHSS score, preoperative tumor volume, tumor location by lobe, tumor location by hemisphere, intraoperative fluorescence, *IDH* mutation status and chemotherapy and radiotherapy. Next, awake craniotomy patients were divided in six subgroups according to age (<70 vs. ≥ 70), preoperative NIHSS score (0-1 vs. ≥ 2), and preoperative KPS (90-100 vs. ≤ 80) and were matched with a 1:2 or 1:4 ratio with patients from the asleep resection group based on the aforementioned factors. Matching ratio was based on the *n* of patients and optimal comparability of both subgroups. Multivariate multiple logistic regressions and multivariate

Table 1: Patient characteristics

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	**Asleep resection (n = 778)**	***p* value**	**Awake craniotomy (n = 128)**	**Asleep resection (n = 384)**	***p* value**
Gender			0.28			0.68
Male	93/140 (66.4)	477/778 (61.3)		86/128 (67.2)	246/384 (64.1)	
Female	47/140 (33.7)	301/778 (38.7)		42/128 (32.8)	138/384 (35.9)	
Age at diagnosis, years			<0.001			0.65
Mean (SD)	57.5 (13.5)	63.6 (10.7)		57.4 (12.9)	60.3 (11.0)	
Median (IQR)	59.0 (50.0-67.3)	65.0 (57.0-71.3)		59.0 (49.0-67.0)	61.0 (53.0-69.0)	
Range	22.0-87.0	20.0-89.0		22.0-87.0	20.0-85.0	
Preoperative KPS			<0.001			0.21
<60	2/140 (1.4)	14/774 (1.8)		1/128 (0.8)	1/384 (0.3)	
60	0/140 (0.0)	43/774 (5.6)		1/128 (0.8)	6/384 (1.6)	
70	6/140 (4.3)	133/774 (17.9)		6/128 (4.7)	35/384 (9.1)	
80	22/140 (15.7)	244/774 (32.8)		25/128 (19.5)	109/384 (28.4)	
90	63/140 (45.0)	266/774 (34.4)		62/128 (48.4)	171/384 (44.5)	
100	47/140 (33.6)	74/774 (9.6)		33/128 (25.8)	62/384 (16.1)	
Median preoperative KPS (IQR)	90 (80-100)	80 (80-90)		90 (80-100)	90 (80-90)	
Preoperative ASA score			0.064			<0.001
I	17/123 (13.8)	89/773 (11.5)		16/113 (14.2)	57/383 (14.9)	
II	64/123 (52.0)	499/773 (64.6)		58/113 (51.3)	252/383 (65.8)	
III	40/123 (32.5)	177/773 (22.9)		39/113 (34.5)	72/383 (18.8)	
IV	1/123 (0.8)	8/773 (1.0)		0/113 (0.0)	2/383 (0.5)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-2)		2 (2-3)	2 (2-2)	

Table 1: Patient characteristics (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	Asleep resection (n = 778)	*p* value	Awake craniotomy (n = 128)	Asleep resection (n = 384)	*p* value
Preoperative NIHSS score			<0.001			0.56
0	63/134 (47.0)	239/774 (30.9)		62/128 (48.4)	163/384 (42.4)	
1	44/134 (32.8)	221/774 (28.9)		41/128 (32.0)	116/384 (30.2)	
2	17/134 (12.7)	159/774 (20.5)		15/128 (11.7)	61/384 (15.9)	
3	3/134 (2.2)	62/774 (8.0)		3/128 (2.3)	21/384 (5.5)	
4	4/134 (3.0)	38/774 (4.9)		4/128 (3.1)	11/384 (2.9)	
>4	3/134 (2.2)	55/774 (7.1)		3/128 (2.3)	12/384 (3.1)	
Median preoperative NIHSS score (IQR)	0 (0-1)	1 (0-2)		1 (0-1)	1 (0-2)	
Tumor location by lobe			0.016			0.12
Frontal	54/140 (38.6)	247/776 (31.8)		51/128 (39.8)	140/384 (36.5)	
Parietal	34/140 (24.3)	189/776 (24.3)		32/128 (25.0)	95/384 (24.7)	
Temporal	49/140 (35.0)	275/776 (35.4)		44/128 (34.4)	126/384 (32.8)	
Occipital	1/140 (0.7)	59/776 (7.6)		1/128 (0.8)	23/384 (6.0)	
Insula	2/140 (1.4)	6/776 (0.8)		0/128 (0.0)	0/384 (0.0)	
Tumor location by hemisphere			<0.001			0.065
Left	112/140 (80.0)	399/788 (50.6)		102/128 (79.7)	274/384 (71.4)	
Right	28/140 (20.0)	389/788 (49.4)		26/128 (20.3)	110/384 (28.6)	
Tumor location by eloquence			<0.001			<0.001
Motor	64/140 (45.7)	418/775 (53.9)		59/128 (46.1)	194/384 (50.5)	
Sensory	10/140 (7.1)	55/775 (7.1)		9/128 (7.0)	25/384 (6.5)	
Language	92/140 (65.7)	334/775 (43.1)		80/128 (62.5)	206/384 (53.6)	
Visual	3/140 (2.1)	168/775 (21.7)		2/128 (1.6)	66/384 (17.2)	
IDH status			0.84			0.48
Wildtype	107/118 (90.7)	449/492 (91.3)		101/106 (95.3)	215/222 (96.8)	
Mutant	11/118 (9.3)	43/492 (8.7)		5/106 (4.7)	7/222 (3.2)	
MGMT status			0.025			0.019
Methylated	45/95 (47.4)	188/533 (35.3)		41/85 (48.2)	76/225 (33.8)	
Unmethylated	50/95 (52.6)	345/533 (64.7)		44/85 (51.8)	149/222 (66.2)	

Table 1: Patient characteristics (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	Asleep resection (n = 778)	*p* value	Awake craniotomy (n = 128)	Asleep resection (n = 384)	*p* value
Surgical adjuncts						
Intraoperative ultrasound	29/140 (20.7)	77/778 (9.9)	<0.001	28/128 (21.9)	78/384 (20.3)	<0.001
Intraoperative fluorescence	27/140 (19.3)	126/778 (16.2)	0.37	29/128 (22.7)	37/384 (9.6)	0.71
Postoperative adjuvant therapy			0.0064			0.041
Radiotherapy only	7/140 (5.0)	88/777 (11.3)		3/128 (2.3)	21/384 (7.4)	
Chemotherapy only	3/140 (2.1)	11/777 (1.4)		3/128 (2.3)	0/384 (0.0)	
Chemoradiotherapy	122/140 (87.1)	580/777 (74.6)		119/128 (93.0)	347/384 (90.4)	
None	8/140 (5.7)	98/777 (12.6)		3/128 (2.3)	16/384 (4.2)	
Reasons for no combined CTx + RTx			0.70			0.45
Due to surgical deficits	1/18 (5.6)	33/192 (17.2)		0/9 (0.0)	13/37 (35.1)	
Due to rapid progression	3/18 (16.7)	30/192 (15.6)		2/9 (22.2)	7/37 (18.9)	
Pre-op already ineligible	6/18 (33.3)	104/192 (54.2)		4/9 (44.4)	9/37 (24.3)	
Patient's wish	2/18 (11.1)	22/192 (11.5)		1/9 (11.1)	6/37 (16.2)	
Due to inclusion in clinical trial	3/18 (16.7)	3/192 (1.6)		1/9 (11.1)	1/37 (2.7)	
Unknown	3/18 (16.7)	0/192 (0.0)		1/9 (11.1)	1/37 (2.7)	
6-week NIHSS-status, pre-op as ref						
Deteriorated	23/128 (18.0)	207/727 (28.5)	0.013	23/125 (18.4)	103/370 (27.8)	0.036
New	12/23 (52.2)	82/207 (39.6)		12/23 (52.2)	48/103 (46.6)	
Worsened	11/23 (47.8)	125/207 (60.4)		11/23 (47.8)	55/103 (53.4)	
Transient	7/23 (30.4)	14/207 (6.8)		7/23 (30.4)	12/103 (11.7)	
Permanent	16/23 (69.6)	191/207 (92.3)		16/23 (69.6)	91/103 (88.3)	
Unknown	0/23 (0.0)	2/207 (1.0)		0/23 (0.0)	0/103 (0.0)	
Improved	35/128 (27.3)	225/727 (30.9)	0.45	31/125 (24.8)	94/370 (25.4)	0.89
Stable	70/128 (54.7)	295/727 (39.2)	0.0029	66/125 (52.8)	173/370 (46.8)	0.24

Table 1: Patient characteristics (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	Asleep resection (n = 778)	*p* value	Awake craniotomy (n = 128)	Asleep resection (n = 384)	*p* value
3-month NIHSS-status, pre-op as ref						
Deteriorated	25/128 (19.5)	191/539 (35.4)	<0.001	25/116 (21.6)	82/330 (24.8)	0.47
New	13/25 (52.0)	87/191 (45.6)		13/25 (52.0)	50/82 (61.0)	
Worsened	12/25 (48.0)	104/191 (54.5)		12/25 (48.0)	32/82 (39.0)	
Improved	39/128 (30.5)	152/539 (28.2)	0.61	34/116 (29.3)	115/330 (34.8)	0.28
Stable	64/128 (50.0)	196/539 (36.4)	0.0050	57/116 (49.1)	133/330 (40.3)	0.10
6-month NIHSS-status, pre-op as ref						
Deteriorated	30/115 (26.1)	206/487 (42.3)	0.0014	30/113 (26.5)	132/315 (41.9)	0.0039
New	16/30 (53.3)	100/206 (48.5)		16/30 (53.3)	69/132 (52.3)	
Worsened	14/30 (46.7)	106/206 (51.5)		14/30 (46.7)	63/132 (47.7)	
Improved	33/115 (28.7)	126/487 (25.9)	0.54	32/113 (28.3)	72/315 (22.9)	0.25
Stable	52/115 (45.2)	155/487 (31.8)	0.0065	51/113 (45.1)	111/315 (35.2)	0.063
Postoperative vascular complications						
None	106/138 (76.8)	583/755 (77.2)	0.92	99/128 (77.3)	302/376 (80.3)	0.47
Major ischemia	3/138 (2.2)	50/755 (6.6)	0.042	2/128 (1.6)	13/376 (3.5)	0.28
Rebleed	3/138 (2.2)	32/755 (4.4)	0.25	1/128 (0.8)	8/376 (2.1)	0.32
Preoperative CE tumor volume, ml			<0.001			0.34
Mean (SD)	42.1 (50.0)	64.8 (53.2)		32.2 (46.8)	46.1 (34.5)	
Median (Q1-Q3)	26.4 (11.6-54.5)	51.8 (27.0-89.0)		22.4 (11.0-48.0)	36.6 (21.6-61.3)	
Range	0.8-208.0	0.4-237.6		0.8-208.0	0.4-204.0	
Postoperative CE tumor volume, ml			0.033			0.0076
Mean (SD)	2.2 (6.1)	8.8 (16.9)		1.9 (5.7)	6.4 (11.6)	
Median (Q1-Q3)	0.1 (0.0-1.6)	2.3 (0.1-9.0)		0.03 (0.0-1.3)	1.8 (0.4-6.4)	
Range	0.0-41.0	0.0-94.6		0.0-41.0	0.0-81.7	
Extent of resection CE tumor, % by volume			<0.001			<0.001
Mean (SD)	95.5 (8.2)	85.5 (19.6)		95.5 (8.3)	85.3 (20.1)	
Median (Q1-Q3)	99.8 (94.8-100.0)	93.8 (97.4-100.0)		99.8 (95.0-100.0)	94.0 (79.5-99.8)	
Range	48.2-100.0	8.9-100.0		48.2-100.0	8.9-100.0	

Table 1: Patient characteristics (continued)

Characteristic	Unmatched cohorts – overall			Matched cohorts (1:3) – overall		
	Awake craniotomy (n = 140)	**Asleep resection (n = 778)**	***p* value**	**Awake craniotomy (n = 128)**	**Asleep resection (n = 384)**	***p* value**
6-week OFO grade	NA	NA				<0.001
OFO 1				59/128 (46.1)	81/384 (21.1)	
OFO 2-3				69/128 (53.9)	303/384 (78.9)	
6-month OFO grade	NA	NA				<0.001
OFO 1				52/128 (40.6)	62/384 (16.1)	
OFO 2-3				76/128 (59.4)	322/384 (83.9)	
Median progression-free survival, months (IQR)	9.0 (5.5-19.0)	7.0 (3.5-15.5)	0.77	10.0 (9.0-12.0)	9.0 (8.0-10.5)	0.21
Median overall survival, months (IQR)	15.0 (10.0-30.8)	13.0 (6.0-23.5)	0.15	20.0 (16.0-31.0)	18.5 (17.0-21.0)	0.042

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the unmatched and matched awake-asleep cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

cox proportional-hazards regressions were used to analyze the predictive value (odds ratios and hazard ratios) of various factors (independent variables) on seven outcomes (dependent variables): (1) NIHSS score deterioration of ≥ 1 point at 6 weeks postoperatively (pre-op as ref); (2) KPS score deterioration of ≥ 10 points at 6 weeks postoperatively (pre-op as ref); (3) proportion of patients who had not received adjuvant chemotherapy and radiotherapy; (4) postoperative residual tumor volume; (5) extent of resection; (6) overall survival and (7) progression-free survival. To prevent the occurrence of the values 0 or 1 for fitted probabilities and non-convergence of the algorithm, a Bayesian generalized linear models was used (*arm* package in *R*). All regression analyses were performed on the overall matched cohort and six matched subgroups to optimize the minimization of confounding, selection bias and causal inference except for the proportion of patients who had received no adjuvant chemotherapy and radiotherapy, for which the regression analyses were performed on the unmatched cohorts since this dependent variable itself was used in the matching procedure. For the presented supplementary analysis, Kaplan-Meier survival curves were plotted for stratified groups based on residual volume or extent of resection for overall survival (OS) and progression-free survival (PFS) (*survival*, *survminer*, *dplyr and ggplot2* packages in *R*). Furthermore, Kaplan-Meier curves were plotted for stratified groups based on OFO grading scale and surgical modality (awake or asleep). Statistical significance between the survival times of different groups and subgroups was tested with the log-rank test.

RESULTS

Patient characteristics of the overall cohort before and after matching can be found in Table 1. After matching, both cohorts were comparable regarding demographics, patient-related, tumor-related and imaging-related characteristics. Additional data concerning the cohorts of the various institutes (eTable 1) and the six subgroups (eTables 2-4) can be found in the Data Supplement.

Association of extent of resection and residual volume with OS and PFS

Overall survival significantly differed between EOR strata for the overall cohort ($p < 0.001$), <70 aged subgroup ($p < 0.001$), NIHSS ≥ 2 subgroup ($p = 0.0096$), KPS 90-100 subgroup ($p = 0.048$) and KPS ≤ 80 subgroup ($p = 0.014$) (Figure 2, Table 2). Furthermore, overall survival was significantly longer for decreasing amounts of residual volume in the overall cohort ($p < 0.001$), <70 aged subgroup ($p < 0.001$), NIHSS ≥ 2 subgroup ($p = 0.025$), KPS 90-100 subgroup ($p = 0.017$) and KPS ≤ 80 subgroup ($p = 0.0065$) (Table 2, Figure 3). Progression-free survival significantly differed between EOR brackets for the overall cohort ($p = 0.0052$), <70 aged subgroup ($p = 0.008$), NIHSS 0-1 subgroup ($p = 0.023$), NIHSS ≥ 2 subgroup ($p = 0.039$) and KPS ≤ 80 subgroup ($p = 0.0088$) (Table 2, Figure 4). Furthermore, progression-free survival differed significantly as a result of various amounts of residual volume in the overall cohort ($p < 0.001$), <70 aged subgroup ($p = 0.0082$), NIHSS

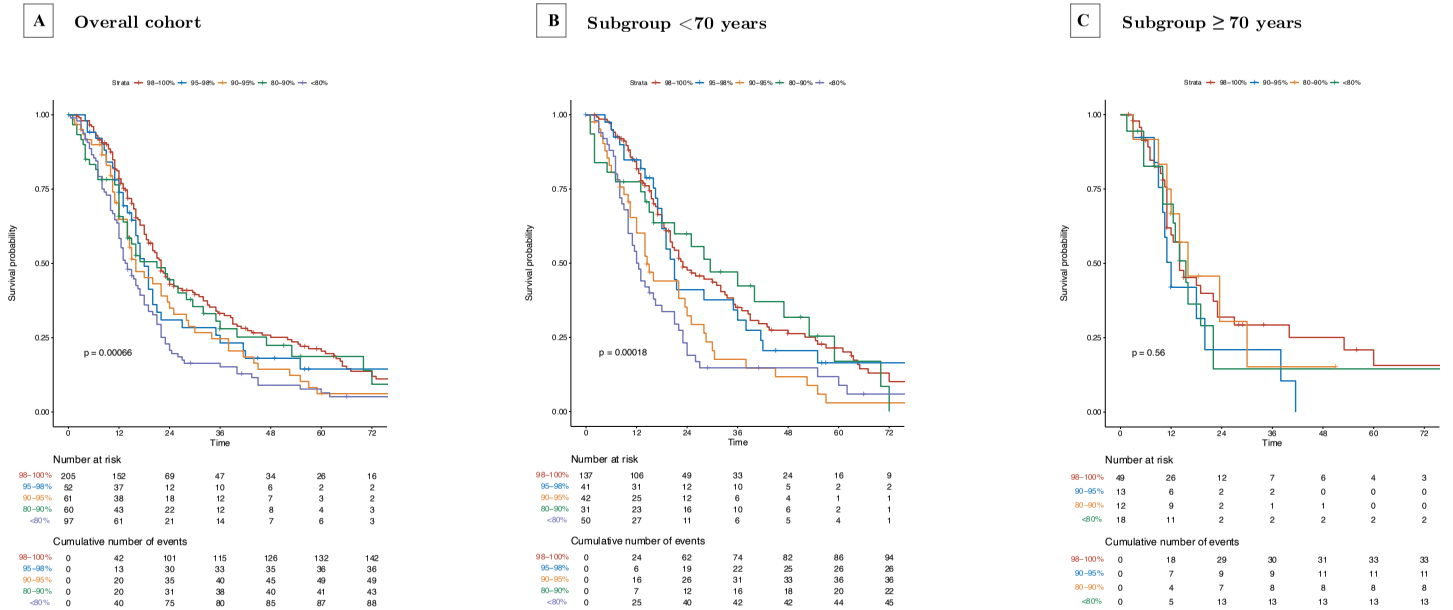

Figure 2: Kaplan-Meier curves for Extent of Resection strata and Overall Survival

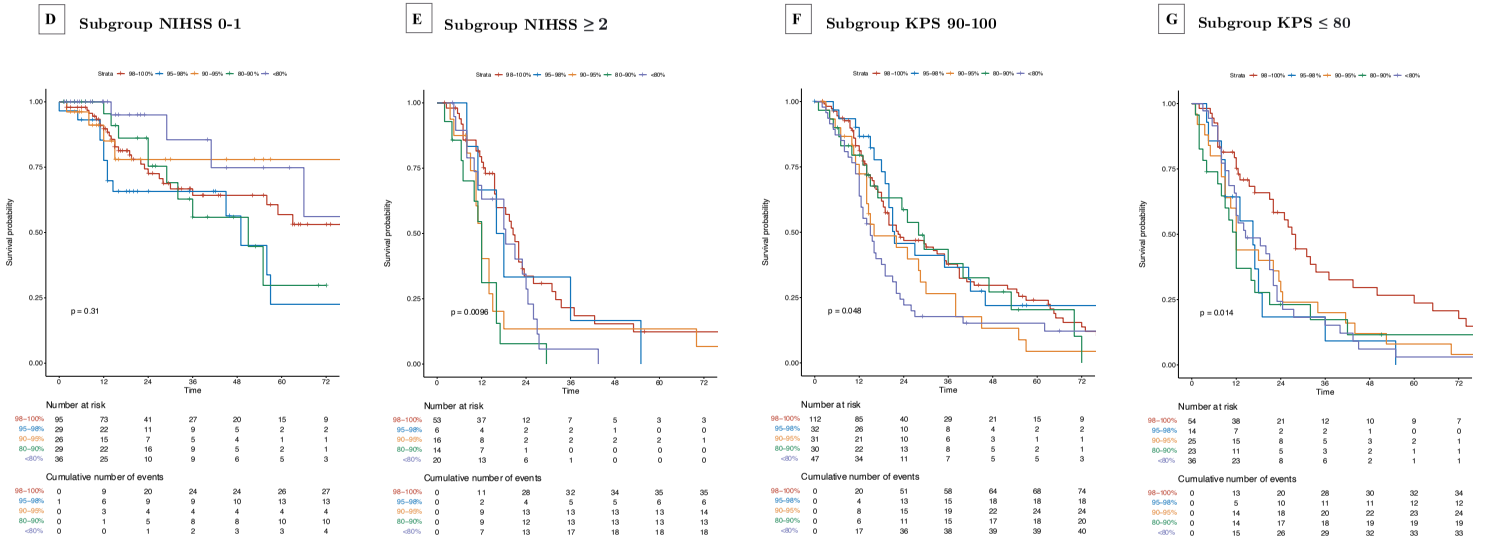

Figure 2: Kaplan-Meier curves for Extent of Resection strata and Overall Survival (continued)

Group characteristics are described in Table 1 and eTables 2, 3 and 4 (Data Supplement). Includes patients in the overall cohort and matched subgroups for age, preoperative NIHSS score and preoperative KPS. Hazard ratios for all subgroup strata are described in Table 2, median survival times are described in Table 3.

Table 2: Survival times for residual tumor volume and extent of resection

Group	Overall [n= 512]	*p*	<70 [n=327]	*p*	≥ 70 [n=95]	*p*	NIHSS 0-1 [n=412]	*p*	NIHSS ≥ 2 [n=125]	*p*	KPS 90-100 [n=285]	*p*	KPS ≤ 80 [n=165]	*p*
Overall survival														
Postoperative CE tumor volume		<0.001		<0.001		0.39		0.31		0.025		0.017		0.0065
0-0.2 ml	22.0 (19.0-26.0)		30.0 (22.0-38.0)		15.0 (12.5-40.0)		77.0 (56.0-NA)		22.0 (16.0-42.5)		23.0 (19.0-39.0)		28.0 (22.0-60.0)	
0.2-1.0 ml	18.0 (14.0-23.5)		20.0 (15.5-26.0)		10.0 (8.0-NA)		45.0 (45.0-NA)		20.5 (15.5-NA)		21.5 (14.0-39.0)		16.5 (15.5-NA)	
1.0-2.0 ml	19.0 (16.0-39.0)		20.0 (18.0-45.0)		12.0 (8.0-NA)		114 (24.0-NA)		16.0 (10.5-NA)		30.0 (18.5-84.0)		19.0 (12.0-NA)	
>2.0 ml	15.0 (13.0-18.0)		15.0 (13.0-23.0)		15.5 (12.0-22.0)		98.0 (66.0-NA)		12.0 (11.0-18.0)		16.5 (15.0-23.0)		12.0 (11.0-20.0)	
Extent of resection CE tumor		<0.001		<0.001		0.56		0.87		0.0096		0.048		0.014
98-100 %	22.0 (19.0-26.0)		23.0 (20.0-33.0)		14.0 (11.0-27.0)		77.0 (56.0-NA)		20.5 (16.0-26.0)		22.5 (19.0-35.5)		27.0 (22.0-43.5)	
95-98 %	18.0 (16.0-22.0)		21.0 (18.0-38.0)		NA 12.0		49.0 (14.5-NA)		17.0 (11.0-NA)		21.5 (20.0-46.0)		16.5 (9.0-NA)	
90-95 %	16.0 (14.0-25.0)		14.5 (12.0-25.0)		(10.0-NA) 16.0		NA 51.0		12.0 (10.5-18.0)		16.0 (14.0-38.0)		12.0 (9.0-24.5)	
80-90 %	21.0 (14.0-32.0)		29.5 (16.0-70.0)		(12.0-NA) 15.5		(32.0-NA) 98.0		12.0 (7.0-NA)		28.0 (17.0-NA)		12.0 (8.0-21.0)	
<80 %	14.0 (12.0-18.0)		12.3 (10.0-18.0)		(12.5-NA)		(66.0-NA)		18.5 (12.0-26.0)		15.0 (12.5-21.0)		14.5 (12.0-23.0)	

Table 2: Survival times for residual tumor volume and extent of resection (continued)

Group	Overall [n= 512]	*p*	<70 [n=327]	*p*	≥ 70 [n=95]	*p*	NIHSS 0-1 [n=412]	*p*	NIHSS ≥ 2 [n=125]	*p*	KPS 90-100 [n=285]	*p*	KPS ≤ 80 [n=165]	*p*
Progression-free survival														
Postoperative CE tumor volume		<0.001		0.0082		0.11		0.025		0.039		0.12		0.012
0-0.2 ml	12.0 (11.0-13.0)		12.0 (11.0-14.5)		9.0 (8.0-11.5)		12.0 (10.5-17.5)		10.0 (6.5-14.0)		12.0 (10.5-14.0)		10.0 (6.0-19.5)	
0.2-1.0 ml	9.0 (6.0-12.0)		10.3 (8.0-16.0)		6.0 (3.0-NA)		11.0 (8.0-17.0)		7.3 (6.0-16.0)		10.0 (8.0-17.0)		9.0 (6.0-16.0)	
1.0-2.0 ml	9.8 (7.0-12.0)		10.8 (9.0-22.0)		6.5 (3.5-NA)		16.0 (9.0-30.0)		10.0 (6.0-43.0)		10.0 (6.0-27.0)		12.0 (6.0-17.0)	
>2.0 ml	8.0 (6.5-9.0)		7.0 (6.0-10.0)		9.0 (17.0-16.0)		9.0 (6.0-12.0)		6.0 (4.0-8.0)		9.0 (7.0-12.0)		7.0 (5.5-9.0)	
Extent of resection CE tumor		0.0052		0.008		0.85		0.023		0.039		0.21		0.0088
98-100 %	11.0 (9.5-12.0)		12.0 (10.0-14.0)		9.0 (6.0-11.0)		11.5 (10.0-14.0)		9.5 (6.0-12.5)		11.8 (10.0-14.0)		10.0 (6.0-16.0)	
95-98 %	9.8 (9.0-12.0)		10.5 (9.0-18.0)		NA 9.3		11.0 (9.0-24.0)		8.8 (6.5-NA)		9.0 (6.0-24.0)		9.0 (7.5-13.0)	
90-95 %	9.5 (7.0-12.0)		9.0 (6.0-12.0)		(5.0-24.0) 9.0		7.0 (5.0-15.0)		8.3 (6.0-36.0)		9.0 (7.0-19.0)		10.0 (6.0-12.0)	
80-90 %	10.8 (6.0-17.0)		12.0 (10.0-24.0)		(3.0-NA) 8.8		16.5 (12.0-28.5)		4.0 (3.0-12.0)		16.0 (12.0-26.0)		7.0 (3.0-11.0)	
<80 %	7.0 (6.0-8.5)		6.0 (4.5-8.5)		(6.0-19.0)		6.0 (5.0-13.5)		4.5 (3.0-14.5)		7.0 (6.0-12.0)		7.0 (3.5-10.0)	

Median survival times in months (95% CI) for strata of residual tumor volume and extent of resection. Statistical significance was evaluated with the log-rank test.
Abbreviations: CI: confidence interval. KPS: Karnofsky Performance Score; NIHSS: National Institute of Health Stroke Scale; CE: contrast enhancing.

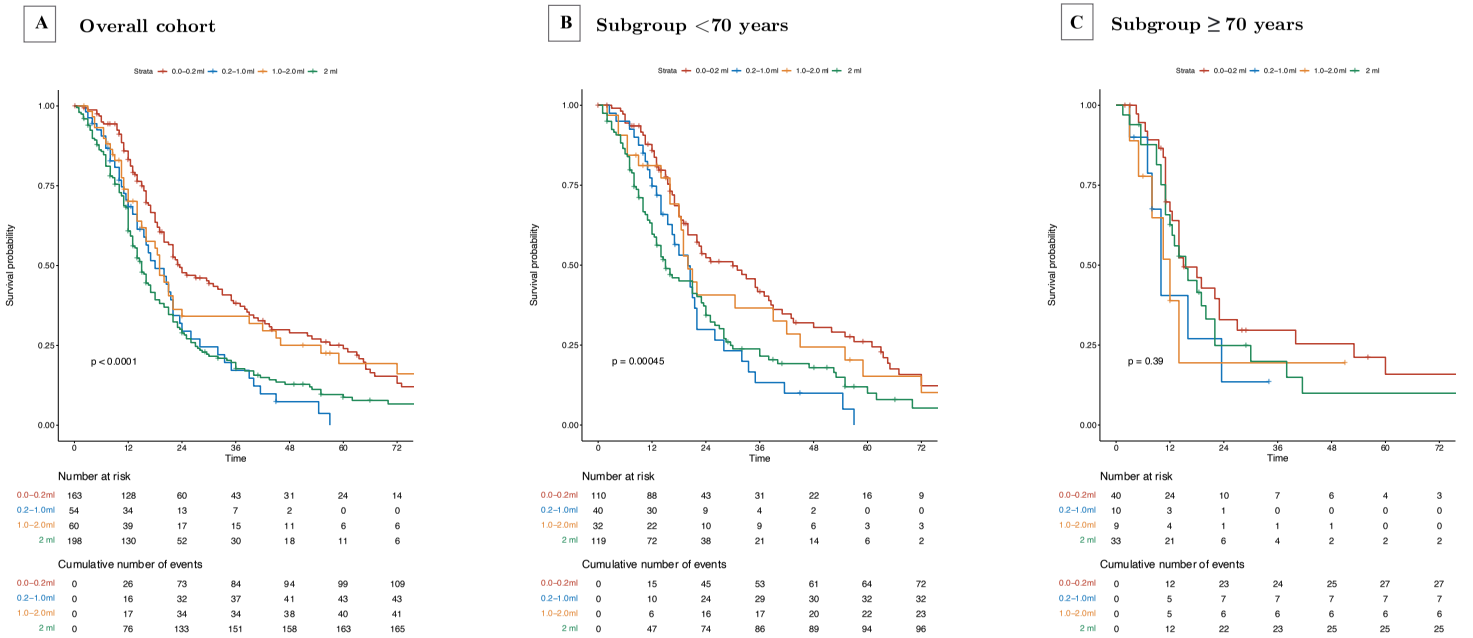

Figure 3: Kaplan-Meier curves for Residual Tumor Volume strata and Overall Survival

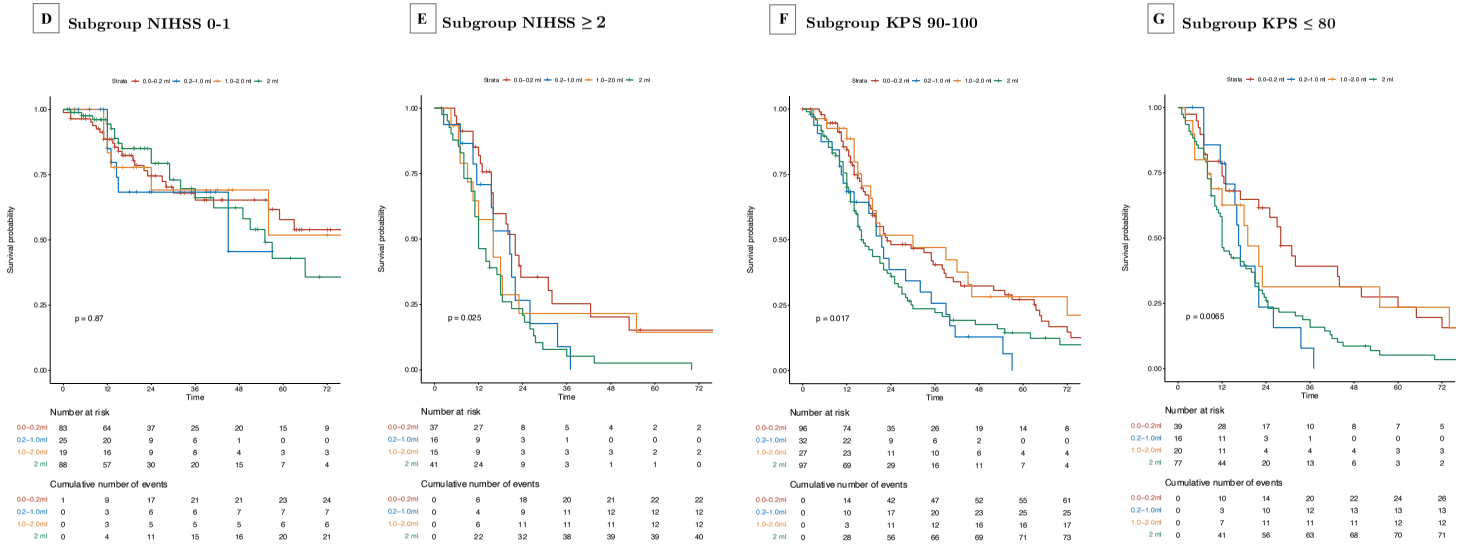

Figure 3: Kaplan-Meier curves for Residual Tumor Volume strata and Overall Survival (continued)

Group characteristics are described in Table 1 and eTables 2, 3 and 4 (Data Supplement). Includes patients in the overall cohort and matched subgroups for age, preoperative NIHSS score and preoperative KPS. Hazard ratios for all subgroup strata are described in Table 2, median survival times are described in Table 3.

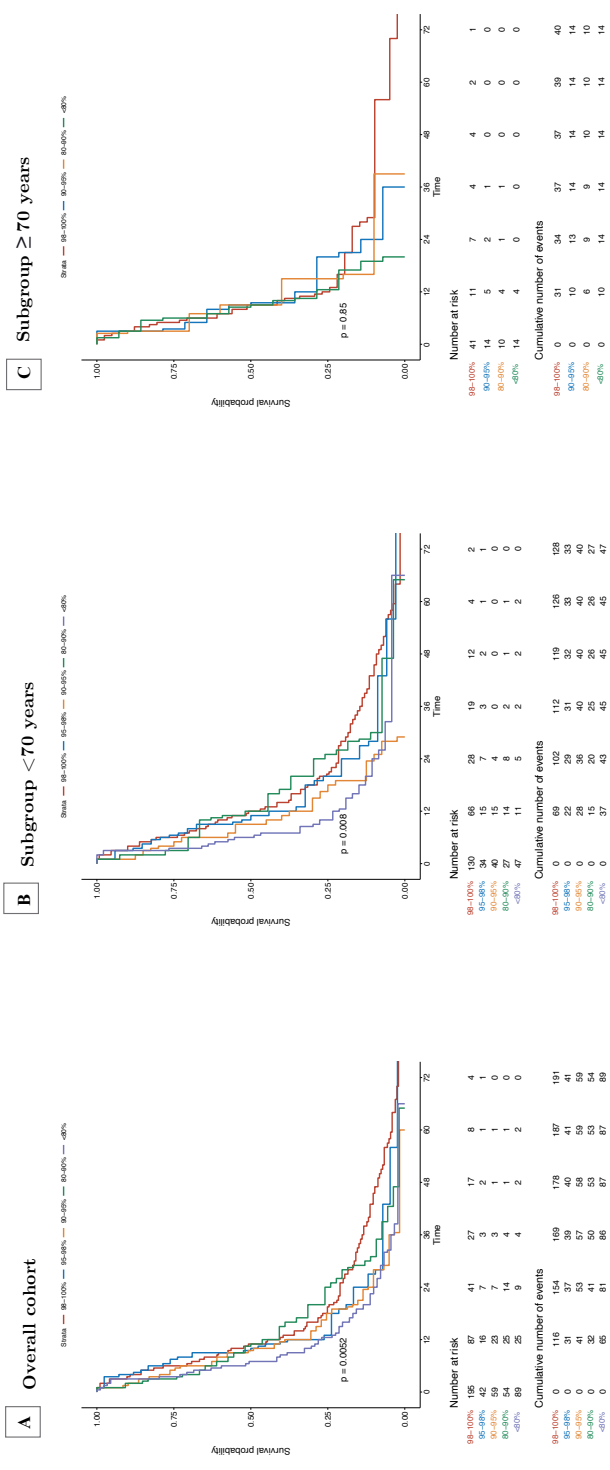

Figure 4: Kaplan-Meier curves for Extent of Resection strata and Progression-Free Survival

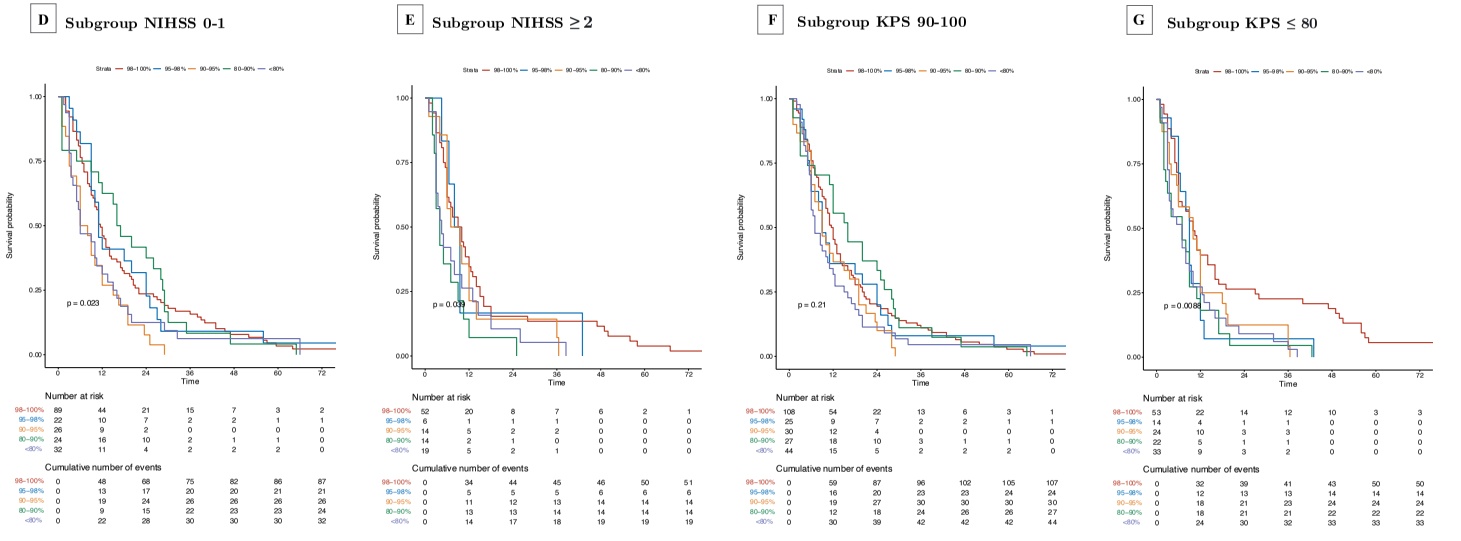

Figure 4: Kaplan-Meier curves for Extent of Resection strata and Progression-Free Survival (continued)

Group characteristics are described in Table 1 and eTables 2, 3 and 4 (Data Supplement). Includes patients in the overall cohort and matched subgroups for age, preoperative NIHSS score and preoperative KPS. Hazard ratios for all subgroup strata are described in Table 2, median survival times are described in Table 3.

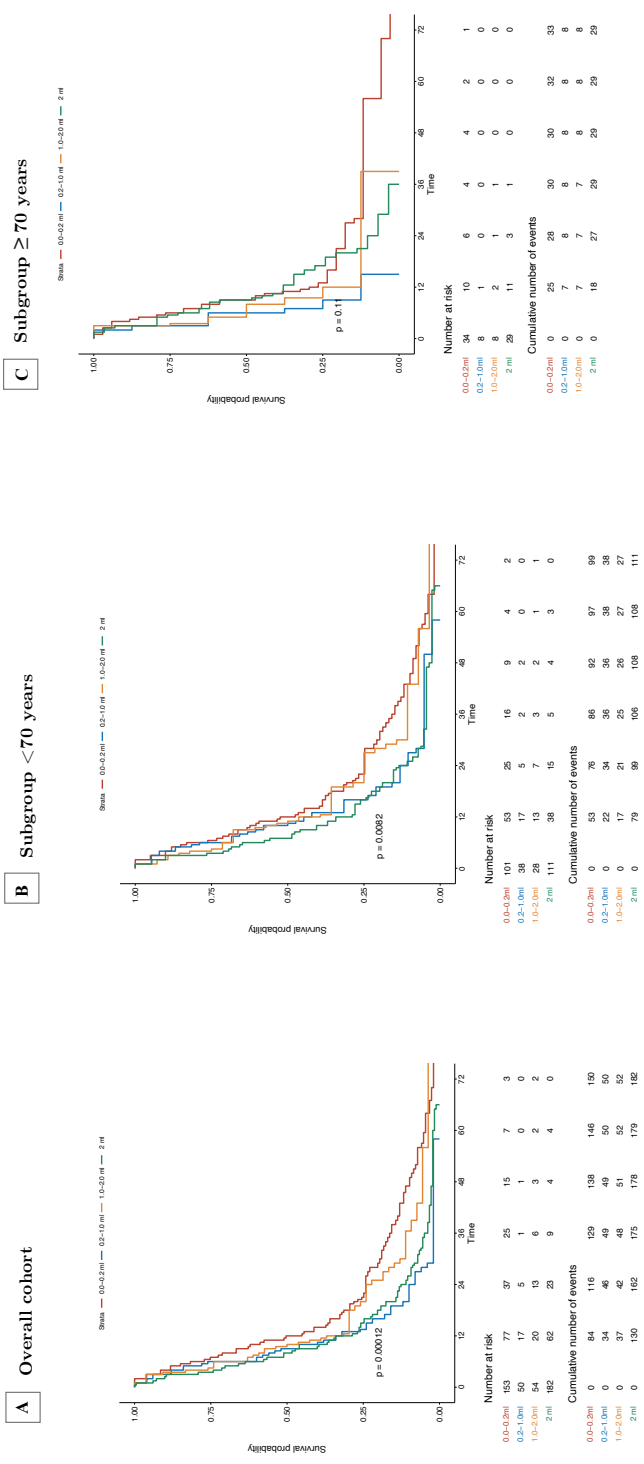

Figure 5: Kaplan-Meier curves for Residual Tumor Volume strata and Progression-Free Survival

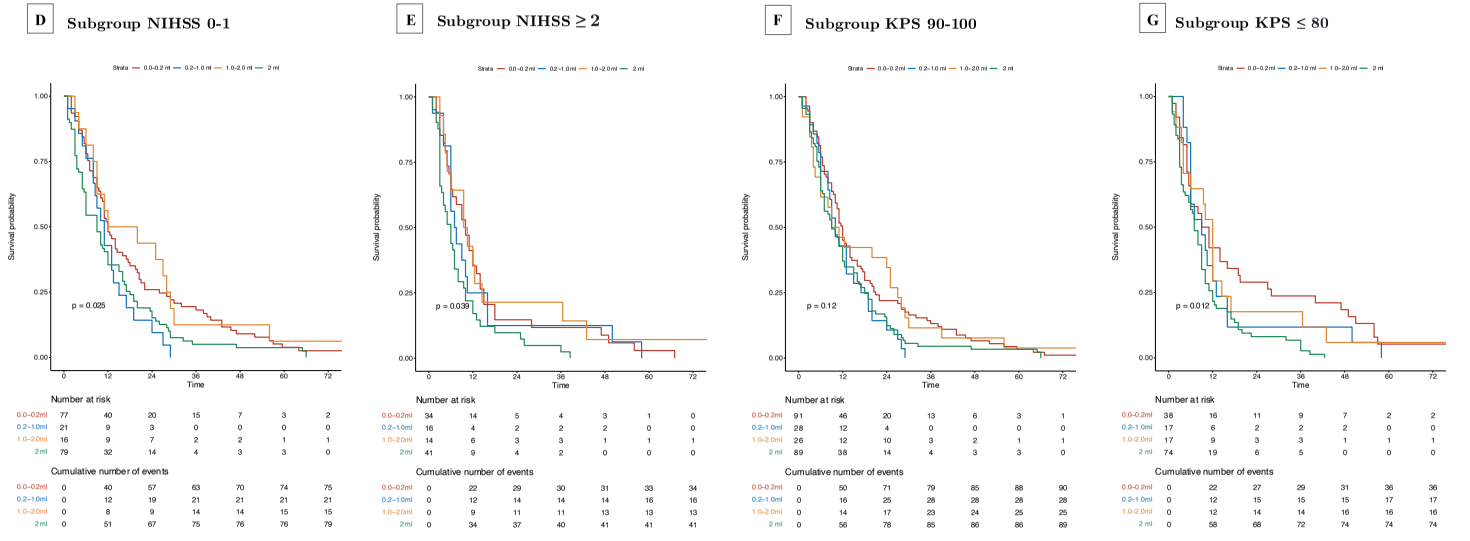

Figure 5: Kaplan-Meier curves for Residual Tumor Volume strata and Progression-Free Survival (continued)

Group characteristics are described in Table 1 and eTables 2, 3 and 4 (Data Supplement). Includes patients in the overall cohort and matched subgroups for age, preoperative NIHSS score and preoperative KPS. Hazard ratios for all subgroup strata are described in Table 2, median survival times are described in Table 3.

0-1 subgroup (p = 0.025), NIHSS ≥ 2 subgroup (p = 0.039), and KPS ≤ 80 subgroup (p = 0.012) (Table 2, Figure 5).

Association of gross-total resection with OS and PFS

Gross-total resection based on residual tumor volume (0.0-0.2 ml) proved to yield superior outcomes in OS for the overall cohort (median 22.0 months [95% CI 19.0-26.0]; p < 0.001), subgroup aged <70 (median 30.0 months [95% CI 22.0-38.0]; p < 0.001), NIHSS ≥ 2 subgroup (median 22.0 [95% CI 16.0-42.5]; p = 0.025), KPS 90-100 subgroup (median 23.0 [95% CI 19.0-39.0]; p = 0.017) and KPS ≤ 80 subgroup (median 28.0 months [95% CI 22.0-60.0]; p = 0.0065) (Table 2). Gross-total resection based on residual tumor volume significantly improved progression-free survival in the overall cohort (12.0 months [95% CI 11.0-13.0]; p < 0.001), and the subgroups aged <70 (median 12.0 months [95% CI 11.0-14.5]; p = 0.0082) and NIHSS ≥ 2 (median 10.0 months [95% CI 6.5-14.0]; p = 0.039) (Table 2).

Association of extent of resection, residual volume and GTR with OS and PFS: Regression analyses

Gross-total resection based on residual volume (0.0-0.2 ml) was significantly predictive for superior overall survival outcomes in the cohort as a whole (HR 0.44, 95% CI 0.23-0.85, p = 0.015), in patients aged ≥ 70 (HR 0.08, 95% CI 0.02-0.30, p = 0.004), and with a preoperative score of NIHSS ≥ 2 (HR 0.07, 95% CI 0.01-0.40, p = 0.003) (Table 2). Residual volume proved to be a better predictor of OS than extent of resection, for which the association with OS was not as congruent across subgroups nor for specific percentages. Residual volume was in none of the subgroups nor in the overall cohort an independent predictor for progression-free survival (PFS). GTR based on EOR was only significantly and positively predictive for PFS in the KPS ≤ 80 subgroup (HR 0.19, 95% CI 0.06-0.65, p = 0.008).

A closer examination of the data of the GLIOMAP study suggests that for some subgroups, other factors might carry a stronger prognostic value than extent or resection or residual tumor volume (eTables 5 and 6, Data Supplement). For example, a good to excellent preoperative KPS score (90-100) was much stronger predictive of overall survival in younger (<70: HR 0.46 [95% CI 0.32-0.67]; p < 0.001) than in older patients (≥ 70: p= 0.90). Moreover, the predictive value of 6-week NIHSS deterioration (HR 1.89 [95% CI 1.30-2.75]; p < 0.001) and 6-week KPS deterioration (HR 2.75 [95% CI 1.88-4.03]; p < 0.001) was much greater in younger patients than in older patients (6-week NIHSS deterioration: p =0.51; 6-week KPS deterioration: p = 0.13). Likewise, in patients with a preoperative KPS of 90-100, preoperative NIHSS score was the dominant prognostic factor (NIHSS 0-1: HR 0.46 [95% CI 0.28-0.76], p = 0.002; NIHSS ≥ 2: HR 1.87 [95% CI 1.21-2.88], p = 0.005) whereas this was not the case in patients with a preoperative KPS of ≤ 80 (NIHSS 0-1: p = 0.26; NIHSS ≥ 2: p = 0.56). Gross-total resection based on residual tumor volume was, just as in the NIHSS ≥

2 subgroup, also predictive for overall survival in patients with a preoperative NIHSS score of 0-1 although this was not significant (HR 0.15 [95% CI 0.02-1.17], p = 0.070). However, mean age (HR 1.03 [95% CI 1.01-1.06]; p = 0.012), motor eloquence (HR 2.28 [95% CI 1.07-4.85]; p = 0.032), and language eloquence (HR 2.99 [95% CI 1.25-7.16]; p = 0.014) were strong prognostics in the NIHSS 0-1 subgroup but not in the NIHSS ≥ 2 subgroup (mean age: p = 0.27, motor eloquence: p = 0.25, language eloquence: p = 0.58). Moreover, 6-week NIHSS and 6-week KPS deterioration had a big prognostic value in the subgroups aged <70, NIHSS 0-1 and KPS 90-100, whereas their value was not as evident in the subgroups aged ≥ 70, NIHSS ≥ 2 and KPS ≤ 80 (eTable 5, Data Supplement).

Extent of resection versus residual volume

We observed a clearer threshold for residual volume than for EOR regarding their association with OS. For example, OS in the overall cohort was longer in the 0.0-0.2 ml subgroup (median 30.0 months, 95% CI 22.0-38.0) than in the 0.2-1.0 ml subgroup (median 18.0 months, 95% CI 14.0-23.5) and the 1.0-2.0 ml subgroup (median 19.0 months, 16.0-39.0 months), which in turn were longer than in the >2 ml subgroup (median: 15.0 months, 95% CI 13.0-23.0). Thus, there was a significant difference in survival times for gross-total resection (maximum 0.2 ml residual volume), >2.0 ml residual volume and the "in-between" group of 0.2-2.0 ml with similar outcomes (p < 0.001). The same pattern could be observed within the subgroups aged <70 (p < 0.001), NIHSS ≥ 2 (p = 0.025) and KPS ≤ 80 (p = 0.017): in those subgroups, the benefit of GTR in OS outcomes was most pronounced. Residual volume was not significantly associated with longer OS outcomes in the subgroups aged ≥ 70 (p = 0.39) and NIHSS 0-1 (p = 0.31) though.

As for the overall association between EOR and OS outcomes, 98-100% EOR resulted in the longest overall survival (median 23.0 months, 95% CI 20.0-33.0). Overall OS outcomes decreased for EOR values of 95-98% (median 21.0, 95% CI 18.0-38.0), 90-95% (median 14.5 months, 95% CI 12.0-25.0) and <80% (median 12.3 months, 95% CI 10.0-18.0), although the 80-90% subgroup did not fit in this pattern (median: 29.5 months, 95% CI 16.0-70.0%). A slightly similar pattern could be observed for EOR in the overall cohort and across the subgroups aged <70 (p < 0.001), NIHSS ≥ 2 (p = 0.0096), KPS 90-100 (p = 0.048) and KPS ≤ 80 (p = 0.014), in which higher EOR percentages were significantly associated with superior OS outcomes. Apart from the overall cohort, the survival benefit of GTR was most pronounced in the NIHSS ≥ 2 (median: 20.5, 95% CI 16.0-26.0) and KPS ≤ 80 subgroups (median: 27.0 months, 95% CI 22.0-43.5). Within the subgroup aged ≥ 70 and NIHSS 0-1 subgroups the association with OS was not as congruent and specific percentages were not significantly associated with longer OS outcomes.

Table 3: Impact of residual tumor volume and extent of resection on postoperative outcomes

Group Characteristic	Overall [n= 512]	*p*	<70 [n=327]	*p*	≥ 70 [n=95]	*p*	NIHSS 0-1 [n=412]	*p*	NIHSS ≥ 2 [n=125]	*p*	KPS 90-100 [n=285]	*p*	KPS ≤ 80 [n=165]	*p*
NIHSS deterioration*	**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds ratio**		**Odds Ratio**	
Postoperative CE tumor volume														
0-0.2 ml	0.33 (0.09-1.18)	0.090	0.21 (0.02-1.77)	0.16	0.83 (0.06-11.0)	0.72	0.20 (0.01-3.77)	0.29	1.20 (0.08-17.7)	0.89	1.03 (0.11-9.81)	0.98	1.87 (0.13-27.0)	0.65
0.2-1.0 ml	0.40 (0.13-1.19)	0.11	0.37 (0.07-2.00)	0.25	2.11 (0.13-34.2)	0.28	1.12 (0.09-13.6)	0.93	0.54 (0.04-8.38)	0.66	1.72 (0.20-14.4)	0.62	0.24 (0.01-4.47)	0.34
1.0-2.0 ml	0.65 (0.25-1.62)	0.36	0.19 (0.04-0.84)	0.033	0.86 (0.06-12.8)	0.97	0.08 (0.00-0.87)	0.053	0.84 (0.06-12.6)	0.90	0.32 (0.03-3.20-)	0.33	1.28 (0.11-14.6)	0.84
>2.0 ml	NA		NA	NA	0.71 (0.06-8.43)	0.79	NA		1.89 (0.10-35.9)	0.67	1.52 (0.16-14.25)	0.72	1.28 (0.10-15.8)	0.85
Extent of resection CE tumor														
98-100 %	0.55 (0.33-0.93)	0.026	2.90 (0.35-24.5)	0.32	1.19 (0.08-18.8)	0.94	5.07 (0.28-105)	0.28	1.22 (0.07-22.6)	0.89	1.15 (0.14-9.63)	0.90	0.44 (0.03-6.68)	0.55
95-98 %	0.75 (0.27-2.00)	0.58	2.16 (0.40-11.3)	0.36	NA 1.55	NA	1.87 (0.16-18.9)	0.60	0.51 (0.02-12.5)	0.68	1.80 (0.24-13.5)	0.57	1.06 (0.10-11.6)	0.96
90-95 %	0.91 (0.42-1.91)	0.80	2.40 (0.70-8.57)	0.17	(0.15-16.4) 0.58	0.32	1.49 (0.27-8.20)	0.64	5.46 (0.34-88.9)	0.23	1.07 (0.16-7.03)	0.95	3.96 (0.43-36.4)	0.22
80-90 %	0.55 (0.25-1.15)	0.12	0.53 (0.12-2.13)	0.38	(0.05-6.71) 0.93	0.97	0.72 (0.15-3.42)	0.69	0.06 (0.00-1.61)	0.09	0.56 (0.07-4.18)	0.57	0.18 (0.01-2.18)	0.18
<80 %	NA		NA		(0.09-10.1)	0.66	NA		1.68 (0.11-25.6)	0.71	0.82 (0.12-5.77)	0.84	2.26 (0.24-21.6)	0.48

Table 3: Impact of residual tumor volume and extent of resection on postoperative outcomes (continued)

Group Characteristic	Overall [n= 512]	*p*	<70 [n=327]	*p*	≥ 70 [n=95]	*p*	NIHSS 0-1 [n=412]	*p*	NIHSS ≥ 2 [n=125]	*p*	KPS 90-100 [n=285]	*p*	KPS ≤ 80 [n=165]	*p*
KPS deterioration[4]	**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds ratio**		**Odds Ratio**	
Postoperative CE tumor volume														
0-0.2 ml	0.76 (0.10-1.79)	0.79	1.10 (0.18-6.68)	0.92	1.72 (0.12-24.0)	0.69	0.65 (0.07-5.95)	0.70	0.43 (0.03-5.31)	0.51	0.80 (0.10-6.49)	0.84	0.82 (0.06-10.7)	0.88
0.2-1.0 ml	0.53 (0.08-1.33)	0.53	0.74 (1.70-3.27)	0.69	0.66 (0.04-10.2)	0.77	0.61 (0.07-5.27)	0.65	0.40 (0.03-5.03)	0.48	0.88 (0.12-6.58)	0.90	0.27 (0.02-4.45)	0.36
1.0-2.0 ml	1.49 (0.31-2.59)	0.70	1.90 (0.51-7.28)	0.34	0.59 (0.04-8.79)	0.70	1.42 (0.15-13.0)	0.76	2.47 (0.22-27.7)	0.46	1.56 (0.20-12.3)	0.67	2.85 (0.24-34.2)	0.41
>2.0 ml	1.66 (0.52-1.88)	0.63	NA		1.44 (0.12-16.7)	0.77	1.81 (0.20-16.6)	0.60	2.33 (0.18-30.6)	0.52	0.92 (0.11-7.43)	0.94	1.36 (0.11-17.0)	0.81
Extent of resection CE tumor														
98-100 %	1.12 (0.25-4.40)	0.91	0.52 (0.08-3.19)	0.49	0.20 (0.01-3.50)	0.27	1.42 (0.16-12.2)	0.75	1.98 (0.16-24.3)	0.59	0.98 (0.14-7.07)	0.98	0.75 (0.06-9.32)	0.82
95-98 %	1.01 (0.28-2.92)	0.99	0.08 (0.17-3.59)	0.76	NA 1.86	NA	0.99 (0.14-7.15)	0.99	0.64 (0.05-8.35)	0.74	0.53 (0.08-3.57)	0.52	2.24 (0.22-23.0)	0.50
90-95 %	0.83 (0.28-1.87)	0.84	0.93 (0.28-3.07)	0.90	(0.16-21.7) 1.40	0.62	1.25 (0.19-8.23)	0.82	0.59 (0.06-5.91)	0.65	1.22 (0.20-7.50)	0.83	0.34 (0.04-3.19)	0.35
80-90 %	0.97 (0.37-2.09)	0.97	1.49 (0.45-4.98)	0.52	(0.12-16.0) 1.26	0.79	0.90 (0.13-6.34)	0.92	2.85 (0.28-28.6)	0.37	1.37 (0.21-8.80)	0.74	1.13 (0.11-11.3)	0.91
<80 %	1.09 (0.32-1.94)	0.92	NA		(0.11-14.7)	0.85	0.63 (0.09-4.54)	0.65	0.52 (0.05-5.05)	0.58	1.11 (0.17-7.15)	0.91	1.41 (0.15-13.0)	0.76

Table 3: Impact of residual tumor volume and extent of resection on postoperative outcomes (continued)

Group Characteristic	Overall [n= 512]	*p*	<70 [n=327]	*p*	≥ 70 [n=95]	*p*	NIHSS 0-1 [n=412]	*p*	NIHSS ≥ 2 [n=125]	*p*	KPS 90-100 [n=285]	*p*	KPS ≤ 80 [n=165]	*p*
No receival adjuvant CTx+RTx	**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds Ratio**		**Odds ratio**		**Odds Ratio**	
Postoperative CE tumor volume														
0-0.2 ml	0.57 (0.08-4.07)	0.58	0.65 (0.07-6.08)	0.71	0.41 (0.04-4.03)	0.45	0.56 (0.08-4.17)	0.58	0.68 (0.06-7.48)	0.75	0.79 (0.09-6.88)	0.83	0.39 (0.04-3.39)	0.39
0.2-1.0 ml	1.70 (0.25-11.5)	0.59	2.56 (0.31-20.9)	0.38	1.68 (0.19-15.0)	0.64	1.33 (0.19-9.17)	0.77	4.83 (0.48-48.9)	0.18	1.54 (0.20-11.9)	0.68	1.85 (0.23-14.9)	0.56
1.0-2.0 ml	1.15 (0.17-7.91)	0.89	0.88 (0.10-7.39)	0.91	0.80 (0.09-7.10)	0.84	1.48 (0.21-10.5)	0.69	0.74 (0.08-7.21)	0.79	1.03 (0.11-9.17)	0.98	1.08 (0.14-8.47)	0.94
>2.0 ml	1.13 (0.16-8.05)	0.90	0.74 (0.08-6.50)	0.78	1.70 (0.19-15.4)	0.64	1.32 (0.18-9.68)	0.79	0.59 (0.06-6.05)	0.66	0.98 (0.11-8.60()	0.98	1.19 (0.14-9.80)	0.87
Extent of resection CE tumor														
98-100 %	0.56 (0.09-3.50)	0.53	0.37 (0.05-2.95)	0.35	0.80 (0.09-6.67)	0.83	0.72 (0.10-4.90)	0.73	0.16 (0.02-1.69)	0.13	0.81 (0.10-6.73)	0.84	0.55 (0.08-3.87)	0.55
95-98 %	0.96 (0.17-5.53)	0.96	0.77 (0.11-5.23)	0.79	1.99 (0.27-14.5)	0.50	0.92 (0.15-5.55)	0.93	1.24 (0.16-9.27)	0.84	1.41 (0.19-10.4)	0.74	0.99 (0.16-6.04)	0.99
90-95 %	0.90 (0.16-5.15)	0.90	0.70 (0.10-4.67)	0.71	0.71 (0.11-4.74)	0.72	1.01 (0.17-6.01)	0.99	0.71 (0.10-5.07)	0.73	0.76 (0.10-6.06)	0.80	0.87 (0.15-5.15)	0.88
80-90 %	1.07 (0.19-6.19)	0.94	2.00 (0.30-13.5)	0.48	0.51 (0.07-3.49)	0.49	0.82 (0.14-5.01)	0.83	1.82 (0.26-12.9)	0.55	0.44 (0.05-4.25)	0.48	1.22 (0.21-7.28)	0.83
<80 %	1.97 (0.35-11.1)	0.44	2.48 (0.38-16.1)	0.34	1.79 (0.27-11.7)	0.54	1.86 (0.32-10.9)	0.49	2.30 (0.33-15.7)	0.39	2.66 (0.36-19.4)	0.34	1.70 (0.29-9.95)	0.55

Table 3: Impact of residual tumor volume and extent of resection on postoperative outcomes (continued)

Group Characteristic	Overall [n= 512]	*p*	<70 [n=327]	*p*	≥ 70 [n=95]	*p*	NIHSS 0-1 [n=412]	*p*	NIHSS ≥ 2 [n=125]	*p*	KPS 90-100 [n=285]	*p*	KPS ≤ 80 [n=165]	*p*
Overall survival	**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**	
Postoperative CE tumor volume														
0-0.2 ml	0.44 (0.23-0.85)	0.015	0.65 (0.29-1.45)	0.30	0.08 (1.33-30.2)	0.004	0.15 (0.02-1.17)	0.070	0.07 (0.01-0.40)	0.003	0.45 (0.17-1.29)	0.12	0.89 (0.21-3.78)	0.88
0.2-1.0 ml	1.00 (0.58-1.72)	0.99	1.32 (0.70-2.50)	0.39	0.78 (0.52-4.37)	0.78	0.30 (0.07-1.36)	0.12	0.17 (0.03-0.98)	0.05	0.82 (0.39-1.73)	0.60	1.98 (0.54-7.27)	0.30
1.0-2.0 ml	0.65 (0.40-1.05)	0.081	1.15 (0.63-2.12)	0.65	1.25 (0.33-4.76)	0.75	0.19 (0.05-0.72)	0.015	0.25 (0.09-0.71)	0.009	0.67 (0.31-1.47)	0.32	0.84 (0.32-2.25)	0.73
>2.0 ml	NA		NA		NA		NA		NA		1.26 (0.86-1.84)	0.24	1.37 (0.87-2.15)	0.23
Extent of resection CE tumor														
98-100 %	0.93 (0.48-1.80)	0.83	0.57 (0.25-1.28)	0.17	11.4 (1.36-94.6)	0.025	22.9 (0.14-245)	0.10	5.17 (0.89-29.9)	0.067	1.15 (0.40-3.33)	0.79	0.37 (0.09-1.49)	0.16
95-98 %	0.83 (0.49-1.42)	0.50	0.44 (0.22-0.88)	0.021	NA 2.12		15.4 (2.90-81.8)	0.001	1.69 (0.44-6.51)	0.44	0.82 (0.33-2.23)	0.66	0.85 (0.30-2.39)	0.76
90-95 %	0.87 (0.57-1.30)	0.49	0.80 (0.47-1.36)	0.41	(0.52-8.41) 0.37	0.29	3.67 (0.73-18.4)	0.12	2.05 (0.76-5.53)	0.16	1.13 (0.61-2.10)	0.69	0.67 (0.32-1.38)	0.28
80-90 %	0.68 (0.46-1.02)	0.061	0.64 (0.36-1.13)	0.12	(0.10-1.43) NA	0.15	4.14 (1.02-16.8)	0.047	2.94 (1.04-8.33)	0.043	0.74 (0.40-1.37)	0.34	0.90 (0.38-2.13)	0.81
<80 %	NA		NA				NA		NA		1.38 (0.88-2.16)	0.17	1.34 (0.82-2.21)	0.25

Table 3: Impact of residual tumor volume and extent of resection on postoperative outcomes (continued)

Group Characteristic	Overall [n= 512]	*p*	<70 [n=327]	*p*	≥ 70 [n=95]	*p*	NIHSS 0-1 [n=412]	*p*	NIHSS ≥ 2 [n=125]	*p*	KPS 90-100 [n=285]	*p*	KPS ≤ 80 [n=165]	*p*
Progression-free survival	**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**		**Hazard ratio**	
Postoperative CE tumor volume														
0-0.2 ml	0.56 (0.31-1.01)	0.054	0.78 (0.38-1.57)	0.48	0.20 (0.04-1.11)	0.065	0.41 (0.15-1.17)	0.095	0.61 (0.14-2.68)	0.52	0.42 (0.17-1.04)	0.060	2.27 (0.68-7.65)	0.18
0.2-1.0 ml	1.18 (0.71-1.96)	0.53	0.93 (0.51-1.70)	0.81	0.89 (0.16-4.91)	0.90	0.72 (0.32-1.63)	0.433	1.22 (0.31-4.85)	0.77	0.73 (0.36-1.46)	0.37	2.95 (0.97-9.01)	0.057
1.0-2.0 ml	0.76 (0.49-1.19)	0.23	0.94 (0.53-1.65)	0.82	0.49 (0.14-1.63)	0.24	0.61 (0.29-1.29)	0.20	0.38 (0.14-1.01)	0.052	0.67 (0.35-1.30)	0.24	1.05 (0.45-2.45)	0.92
>2.0 ml	NA		NA		NA		NA		NA		1.22 (0.88-1.69)	0.24	1.42 (0.93-2.16)	0.11
Extent of resection CE tumor														
98-100 %	0.95 (0.52-1.73)	0.87	0.68 (0.32-1.44)	0.31	3.28 (0.38-28.1)	0.28	1.07 (0.37-3.13)	0.90	1.03 (0.22-4.76)	0.97	1.38 (0.54-3.54)	0.50	0.19 (0.06-0.65)	0.008
95-98 %	0.80 (0.47-1.35)	0.40	0.68 (0.36-1.30)	0.24	NA 2.42		0.78 (0.35-1.76)	0.56	1.92 (0.50-4.85)	0.34	1.07 (0.48-2.39)	0.88	0.47 (0.18-1.25)	0.13
90-95 %	0.87 (0.60-1.27)	0.47	0.98 (0.59-1.65)	0.95	(0.73-8.08) 0.77	0.15	1.20 (0.62-2.32)	0.60	0.57 (0.23-1.44)	0.24	1.13 (0.64-1.98)	0.68	0.41 (0.21-0.80)	0.010
80-90 %	0.72 (0.49-1.04)	0.081	0.70 (0.40-1.22)	0.21	(0.26-2.28) NA	0.64	0.49 (0.26-0.91)	0.025	3.01 (1.21-7.47)	0.018	0.64 (0.37-1.10)	0.11	0.79 (0.38-1.62)	0.52
<80 %	NA		NA						NA		1.19 (0.79-1.79)	0.41	1.52 (0.94-2.47)	0.088

Impact of residual tumor volume and extent of resection on NIHSS deterioration, KPS deterioration and receival of no adjuvant chemotherapy and radiotherapy was evaluated using multiple multivariate logistic regression. Impact on overall survival and progression-free survival was evaluated using multivariate Cox proportional-hazards regression modelling.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

*NIHSS deterioration of ≥ 1 point at 6 weeks postoperatively. ¶KPS deterioration of ≥ 10 points at 6 weeks postoperatively.

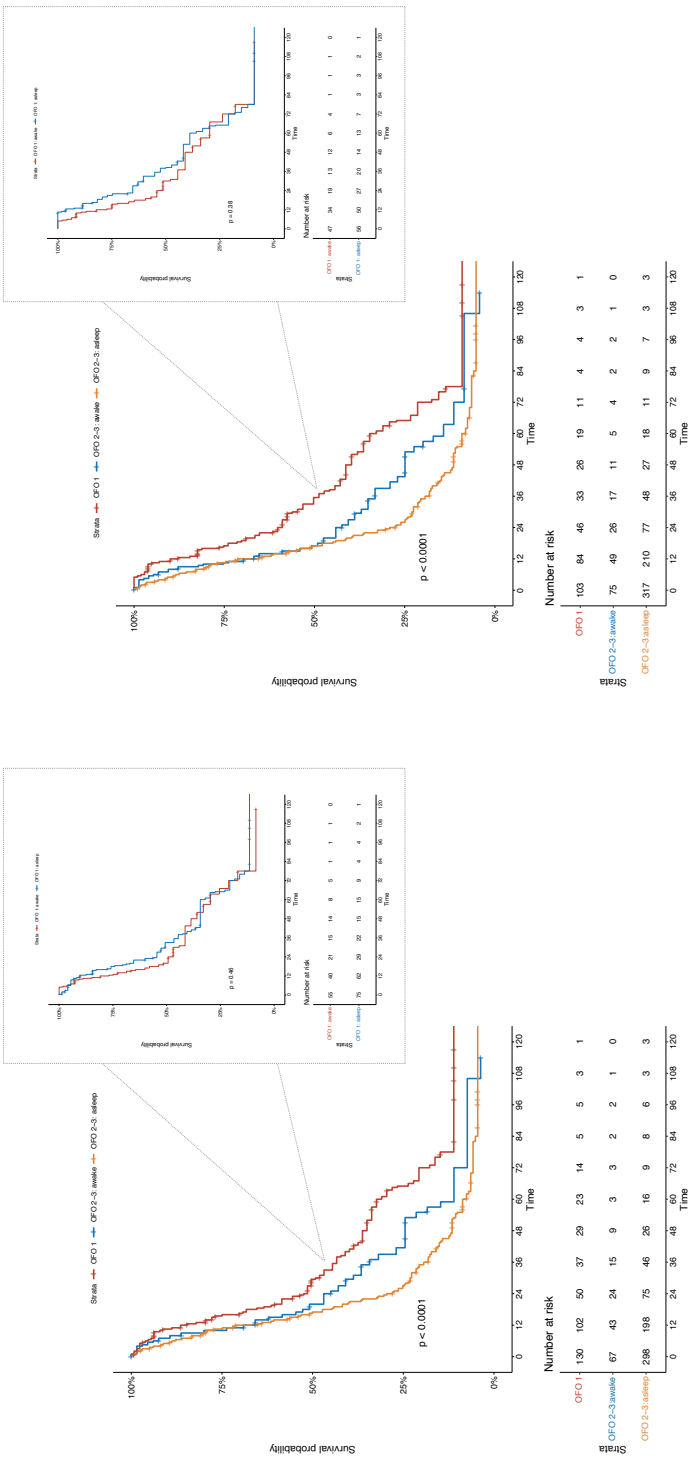

Figure 6: Kaplan-Meier curves stratified by Onco-Functional Outcome (OFO) grading scale
Group characteristics and outcomes are described in Table 1. Includes patients in the overall matched cohort and matched subgroups for age, preoperative NIHSS score and preoperative KPS.

Overall, median PFS in patients with a residual tumor volume of 0.0-0.2 ml was 12.0 months (95% CI 11.0-13.0), which was significantly longer than the subgroups with a residual tumor volume of 0.2-1.0 ml (median: 9.0 months, 95% CI 6.0-12.0), 1.0-2.0 ml (median: 9.8 months, 95% CI 7.0-12.0) and >2 ml (median: 8.0 months, 95% CI 6.5-9.0) ($p < 0.001$). GTR proved to yield significantly superior PFS in the subgroups aged <70 (median: 12.0 months [95% CI 11.0-14.5]; $p = 0.0082$) and NIHSS ≥ 2 (median: 10.0 months [95% CI 6.5-14.0]; $p = 0.039$). Likewise, higher EOR values were associated with a longer PFS in the overall cohort (98-100%: median: 11.0 months [95% CI 9.5-12.0]; 0.0052) and the subgroups aged <70 (98-100%: median: 12.0 months [95% CI 10.0-14.0]; $p = 0.008$), NIHSS ≥ 2 (98-100%: median: 9.5 months [95% CI 6.0-12.5]; $p = 0.039$) and KPS ≤ 80 (98-100%: median: 10.0 months [95% CI 6.0-16.0]; $p = 0.0088$).

Association of extent of resection or residual volume with functional outcomes

Table 3 summarizes the results from the multiple multivariate regression (NIHSS deterioration, KPS deterioration and receipt of adjuvant therapy) and the multivariate cox proportional-hazards regression (overall survival, progression-free survival). Overall, an extent of resection of 98-100% significantly decreased the risk of NIHSS deterioration at 6 weeks postoperatively (OR 0.55, 95% CI 0.33-0.93, $p = 0.026$), while gross-total resection based on residual tumor volume (0.0-0.2 ml) also lead to a reduction of this risk, although this was not significant (OR 0.33, 95% CI 0.09-1.18, $p = 0.090$). In none of the subgroups a significant association between extent of resection or residual tumor volume and NIHSS deterioration could be observed except for 1.0-2.0 ml residual tumor volume in the subgroup <70 years (OR 0.19, 95% CI 0.04-0.84, $p = 0.033$). Extent of resection nor residual volume significantly impacted postoperative KPS deterioration or receipt of adjuvant therapy for the cohort as a whole or across subgroups (Table 3).

Combined impact of GTR and preservation of neurological function on OS

Moreover, we analyzed the combined effect of gross-total resection based on residual volume with preservation or improvement of postoperative NIHSS (with preoperative NIHSS as reference) at both 6 weeks and 6 months. We can refer to this merged outcome as the "onco-functional outcome" which we have described more elaborately in an earlier publication [11]. In general, OFO 1 applies to patients in which both GTR are reached and neurological functioning are preserved or improved postoperatively. OFO 2 and OFO 3 apply to patient subgroups in which one of these two goals is not achieved. OFO 2 applies to patients in which neurological functioning is preserved, but GTR is not reached, whereas OFO 3 applies to patients in which GTR is reached, but postoperative neurological deficits have occurred (1 point or more increase in NIHSS). The OFO classification can be used at 6 weeks or 6 months postoperatively.

Overall, we found that OFO 1 status at 6 weeks postoperatively was achieved in 46.1% in the awake group and in 21.1% in the asleep group (p<0.001). Furthermore, the median OS in the OFO 1 group was 29.5 months [95% CI 20.0-41.0], which was significantly longer than the OFO 2-3 group with awake mapping (median OS 20.0 months [95% CI 15.0-35.0]) and the OFO 2-3 group with asleep mapping (median OS 17.0 months [95% CI 15.0-19.0]) (p<0.0001).

OFO 1 status at 6 months postoperatively was achieved in 40.6% in the awake group and in 16.1% in the asleep group (p<0.001). Furthermore, the median OS in the OFO 1 group was 35.5 months [95% CI 24.0-53.0], which was significantly longer than the OFO 2-3 group with awake mapping (median OS 17.0 months [95% CI 14.0-31.0]) and the OFO 2-3 group with asleep mapping (median OS 17.0 months [95% CI 15.0-19.0]) (p<0.0001).

DISCUSSION

Extent of resection and residual tumor volume are both important metrics to assess tumor reduction and have been associated with survival outcomes [1-10]. As described by Karschnia *et al* [14], there is no consensus - definition of the concepts of partial resection, subtotal resection, near total resection, gross-total resection and supramaximal resection. For gross-total resection, definitions ranged from 90-100% [15,16], 96-100% [17], 97-100% [18] to 100% [19-24], while for near-total resection most reported values were ≥ 95% EOR or ≤ 1 cm^3 (1 ml) residual volume [10, 24, 25]. Previous studies suggested that patients who had ≥ 95% EOR had better survival outcomes than patients with ≤ 95% EOR [12,17], but as Karschnia *et al* pointed out it remains virtually unknown if patients with an EOR of 95-98% experience similar or different survival outcomes from patients with EOR values above or under this range. Consequently, we addressed the question if patients with different ranges of EOR or residual volume above that "minimum threshold" would experience significantly different survival outcomes. As for minimum thresholds of EOR or residual volume that would lead to distinctly improved survival outcomes, the generally accepted values are 80% and 2-5 ml respectively [4, 9, 10, 21] which we therefore used as cut-off points in the presented study. We defined gross-total resection as 0.0-0.2 ml (0.0-0.2 cm^3) residual tumor volume (which is in line with the value used by Stummer *et al* [26] in their 5-ALA trial [0.175 ml/0.175 cm^3]) or an extent of resection of 98-100%, which is comparable with values that are used in previous studies [15-24].

This is, to our knowledge, the first study that evaluates the prognostic value of different values of extent of resection and residual tumor volume in patients with eloquent glioblastoma in general and in patient subgroups. Furthermore, we combined these survival analyses with measures of postoperative neurological functioning (NIHSS) and KPS.

For the GLIOMAP study we restricted our cohort to primary glioblastoma resections in or near eloquent areas that were performed between 2010 and 2020 for a contemporary assessment of the impact of extent of resection and residual tumor volume. We found that in the overall cohort and across subgroups, extent of resection and residual tumor volume were strongly associated and predictive for survival outcomes, whereas the strongest associations were found between residual tumor volume and overall survival. A higher extent of resection or alternatively a lower residual tumor volume significantly improved OS and PFS across all subgroups except in the NIHSS 0-1 subgroup for overall survival and in the subgroups aged ≥ 70 and KPS 90-100 for progression-free survival. Moreover, multivariate regression analyses suggested that gross-total resection based on residual volume (0.0-0.2 ml) or extent of resection (98-100%) was independently predictive for overall survival in the overall cohort, in patients aged ≥ 70, in patients with a preoperative NIHSS score of ≥ 2 and with a preoperative KPS of ≤ 80. Besides, GTR based on EOR was significantly predictive for PFS in the KPS ≤ 80 subgroup.

As for surgical safety, the regression analyses showed that an extent of resection of 98-100% significantly decreased the overall risk of neurological (NIHSS) deterioration at 6 weeks postoperatively (OR 0.55, 95% CI 0.33-0.93, p = 0.026). However, gross-total resection was not significantly predictive for postoperative KPS deterioration or receipt of adjuvant therapy.

An important finding was the fact that patients aged ≥ 70 or patients with an impeded preoperative NIHSS score (≥ 2) or KPS (≤ 80) proved to have the most benefit from gross-total resection as indicated by the survival analyses and confirmed by the multivariate regression analyses. A closer look at the GLIOMAP data might offer us a few possible reasons.

A first reason might be that in younger patients (<70) or patients with a better preoperative status (NIHSS 0-1, KPS 90-100), other factors might carry a stronger prognostic value: preoperative KPS score and postoperative NIHSS and KPS scores in younger patients, preoperative NIHSS score in patients with a preoperative KPS of 90-100 and age and motor/language eloquence in patients with a preoperative NIHSS score of 0-1. This suggests that in these subgroups of patients, tumor reduction is important (as indicated by the survival analyses), but preventing postoperative NIHSS and KPS worsening (<70 subgroup, NIHSS 0-1 subgroup) or optimizing preoperative neurological functioning (KPS 90-100 subgroup) might be of utmost importance to improve survival outcomes. We therefore stress the importance of awake mapping, which we found to be an excellent tool in the subgroups aged <70 and preoperative NIHSS 0-1 to maintain optimum KPS and NIHSS scores which in turn would favor their survival [27]. Last, we found that 6-week NIHSS and 6-week KPS deterioration were of greater prognostic importance in the subgroups aged <70, NIHSS 0-1

and KPS 90-100 than in the subgroups aged ≥ 70, NIHSS ≥ 2 and KPS ≤ 80, suggesting that in the former subgroups surgical safety might be more important in overall survival, while removing as much of the tumor as possible is in the latter.

A second reason might be the assumption that the impact of surgical extent of resection or residual tumor volume becomes bigger in the groups where less adjuvant chemotherapy and radiotherapy is being given – typically older patients, or patients with an impaired performance or preoperative neurological deficits. This explanation would be in line with the findings of Lacroix *et al* which they describe in their 2001 paper, according to which a higher extent of resection was required in untreated glioblastoma patients [with adjuvant therapy] than in the treated ones to yield a statistical difference in survival outcomes [3].

To our knowledge, this study is the first to demonstrate the evident prognostic value of achieving OFO 1 status in glioblastoma patients: reaching GTR in combination with preservation of postoperative neurological functioning. Both OFO models at 6 weeks and 6 months postoperatively show significant longer overall survival times in the OFO 1 subgroups than in the OFO 2-3 subgroups. Besides, our data showed that it did not matter if OFO 1 status was achieved with awake or asleep mapping.

Limitations

This study is subject to several limitations. Since the presented study has been carried out retrospectively, we strived to minimize the risk of selection bias and confounding by combining propensity score matching with multiple multivariate logistic and cox regression analyses. Moreover, we set our cut-off values for GTR at 98% for EOR and 0.2 ml for residual tumor volume. We therefore did not analyze potential differences in 98-99% and 100% extent of resection of the tumor, which might differ as reported by Sanai *et al* [1]. Last, we did not evaluate the impact of resecting the non-contrast-enhancing (NCE) part of the tumor, which has been shown by Molinaro *et al* to improve overall survival in younger patients, regardless of *IDH* or MGMT status [10]. Evaluation of the value of 100% vs. 99% vs. 98% CE tumor resection with additionally NCE tumor resection in glioblastoma patient subgroups differing in age, preoperative KPS and NIHSS scores should be the focus of future scientific efforts.

CONCLUSIONS

This study is the first, to our knowledge, to demonstrate the impact of extent of resection, residual tumor volume and gross-total resection in various eloquent glioblastoma subgroups. We found that a higher extent of resection or lower residual tumor volume significantly im-

proved OS and PFS for all subgroups except in the NIHSS 0-1 subgroup for overall survival and in the subgroups aged ≥ 70 and KPS 90-100 for progression-free survival. Gross-total resection significantly decreased the overall risk of neurological deterioration at 6 weeks postoperatively and was especially beneficial for overall survival improvement in patients aged ≥ 70, in patients with a preoperative NIHSS score of ≥ 2 and with a preoperative KPS of ≤ 80. Moreover, the achievement of OFO 1 at 6 weeks and 6 months postoperatively led to significant improved survival outcomes. To prevent postoperative neurological deficits and achieve OFO 1 status, mapping techniques such as awake craniotomy can be employed by the surgeon to pursue GTR safely.

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DATA SUPPLEMENT

eMethods 1: Details and Cohorts

Data collection

All patients with glioblastoma surgery between January 2010 and October 2020 at the Erasmus Medical Center, Haaglanden Medical Center, University Hospital Leuven and Brigham and Women's Hospital were screened for eligibility (n = 4075). Inclusion criteria were (1) resection (excluding biopsy), (2) histopathological diagnosis of primary glioblastoma (excluding grade II/III gliomas with malignant transformation and recurrent glioblastomas), (3) eloquent or near-eloquent location of the tumor, (4) unifocal enhancing lesion (excluding multifocal enhancing lesions), (4) availability of clinical and radiological data in electronic patient file. After exclusion of 3157 patients, 918 patients with tumor resection for primary, eloquent glioblastoma were eligible for inclusion in the analysis subsets. Collected data included patient demographics, preoperative functioning (KPS, NIHSS), comorbidities (ASA), tumor related factors (location by lobe and hemisphere), molecular factors (IDH status, MGMT status), surgical factors (intraoperative electrophysiological mapping, intraoperative ultrasound, intraoperative fluorescence), adjuvant therapy, postoperative functioning (KPS and NIHSS at 6 weeks, 3 months and 6 months), volumetric tumor data and survival data. Tumor volumes were assessed both preoperatively and postoperatively with volumetric measurements on T1-weighted post-gadolinium images based on the contrast-enhancing (CE) part of the tumor. Extent of resection was calculated as (pre-operative tumor volume – post-operative tumor volume)/pre-operative tumor volume x 100%. Preoperative scans were obtained within 24 hours prior to resection and postoperative scans were obtained within 72 hours after resection. Postoperative T1-weighted post-gadolinium MR-images were compared with DWI-sequences to exclude induced edema or ischemia in the tumor volumetrics. OS and PFS were analyzed for the overall matched cohorts and six matched cohort subgroups. OS was defined as the date of tumor resection until death or last follow up whereas PFS was defined as date of tumor resection until radiological recurrence of the tumor on T1-contrast MR-images.

eTable 1: Demographic table for Erasmus MC, Haaglanden MC, UZ Leuven and Brigham Cohorts

Characteristic	EMC-Cohort (n = 382)	HMC-Cohort (n = 354)	Leuven-Cohort (n = 111)	Boston-Cohort (n = 71)	*p* value
Gender					0.0434
Male	236/382 (61.2)	221/354 (62.4)	78/111 (70.3)	35/71 (49.3)	
Female	146/382 (38.2)	133/354 (37.6)	33/111 (29.7)	36/71 (50.7)	
Age at diagnosis, years					0.75
Mean (SD)	61.2 (10.9)	64.8 (11.1)	60.5 (11.8)	63.2 (12.7)	
Median (IQR)	62.5 (54-70)	67.0 (58.0-73.0)	64.0 (52.0-69.0)	66.0 (56.0-70.0)	
Range	22.0-82.0	25.0-89.0	20.0-85.0	23.0-87.0	
Preoperative KPS					<0.001
<60	4/382 (1.0)	8/354 (2.3)	1/111 (0.9)	2/61 (3.3)	
60	19/382 (5.0)	23/354 (6.5)	2/111 (1.8)	0/61 (0.0)	
70	76/382 (19.9)	49/354 (13.8)	7/111 (6.3)	7/61 (11.5)	
80	122/382 (31.9)	105/354 (30.0)	26/111 (23.4)	18/61 (29.5)	
90	108/382 (28.3)	138/354 (39.0)	53/111 (47.7)	32/61 (52.5)	
100	53/382 (13.9)	31/354 (8.8)	22/111 (19.8)	2/61 (3.3)	
Median preoperative KPS (IQR)	80 (70-90)	80 (80-90)	90 (80-90)	90 (80-90)	
Preoperative ASA score					<0.001
I	67/381 (17.6)	33/354 (9.3)	6/111 (5.4)	0/50 (0.0)	
II	257/381 (67.5)	244/354 (68.9)	52/111 (46.8)	11/50 (22.0)	
III	56/381 (14.7)	75/354 (21.2)	51/111 (45.9)	35/50 (70.0)	
IV	1/381 (0.3)	2/354 (0.6)	2/111 (1.8)	4/50 (8.0)	
Median preoperative ASA score (IQR)	2 (2-2)	2 (2-2)	2 (2-3)	2 (1-3)	
Preoperative NIHSS score					<0.001
0	138/382 (36.1)	115/354 (32.5)	21/111 (18.9)	28/61 (45.9)	
1	125/382 (32.7)	95/354 (26.8)	28/111 (25.2)	17/61 (27.9)	
2	82/382 (21.5)	61/354 (17.2)	21/111 (18.9)	12/61 (19.7)	
3	19/382 (5.0)	31/354 (8.8)	14/111 (12.6)	1/61 (1.6)	
4	8/382 (2.1)	23/354 (6.5)	10/111 (9.0)	1/61 (1.6)	
>4	10/382 (2.6)	29/354 (8.2)	17/111 (15.3)	2/61 (3.3)	
Median preoperative NIHSS score (IQR)	1 (0-2)	1 (0-2)	2 (1-3)	1 (0-2)	

eTable 1: Demographic table for Erasmus MC, Haaglanden MC, UZ Leuven and Brigham Cohorts (continued)

Characteristic	EMC-Cohort (n = 382)	HMC-Cohort (n = 354)	Leuven-Cohort (n = 111)	Boston-Cohort (n = 71)	*p* value
Tumor location by lobe					<0.001
Frontal	120/382 (31.4)	118/354 (33.3)	33/111 (29.7)	30/71 (42.3)	
Parietal	84/382 (22.0)	95/354 (26.8)	34/111 (30.6)	10/71 (14.1)	
Temporal	152/382 (39.8)	126/354 (35.6)	26/111 (23.4)	29/71 (40.8)	
Occipital	26/382 (6.8)	15/354 (4.2)	18/111 (16.2)	2/71 (2.8)	
Tumor location by hemisphere					0.0039
Left	219/382 (57.3)	176/354 (49.7)	65/111 (58.6)	51/71 (71.8)	
Right	163/382 (42.7)	178/354 (50.3)	46/111 (41.4)	20/71 (28.2)	
Tumor location by eloquence					<0.001
Motor	190/382 (49.7)	211/354 (59.6)	58/111 (52.3)	23/69 (33.3)	
Sensory	58/382 (15.2)	61/354 (17.2)	11/111 (9.9)	31/69 (44.9)	
Language	185/382 (48.4)	154/354 (43.5)	48/111 (43.2)	4/69 (5.8)	
Visual	79/382 (20.7)	61/354 (17.2)	30/111 (27.0)	1/69 (1.4)	
IDH status					0.0056
Wildtype	157/164 (95.7)	248/286 (86.7)	88/93 (94.6)	63/68 (92.6)	
Mutant	7/164 (4.2)	38/286 (13.3)	5/93 (5.4)	5/68 (5.8)	
MGMT status					<0.001
Methylated	99/189 (52.4)	93/344 (27.0)	10/29 (34.5)	31/66 (47.0)	
Unmethylated	90/189 (47.6)	251/344 (73.0)	19/29 (65.5)	35/66 (53.0)	
Mapping and surgical adjuncts					
Intraoperative mapping	41/382 (10.7)	24/354 (6.8)	27/111 (24.3)	45/71 (63.4)	<0.001
Intraoperative ultrasound	73/382 (19.1)	0/354 (0.0)	0/111 (0.0)	33/71 (46.5)	<0.001
Intraoperative fluorescence	25/382 (6.5)	17/354 (4.8)	110/111 (99.1)	3/71 (4.2)	<0.001
Postoperative adjuvant therapy					0.0039
Radiotherapy only	45/382 (11.8)	37/354 (10.5)	7/111 (6.3)	6/70 (8.6)	
Chemotherapy only	7/382 (1.8)	3/354 (0.8)	4/111 (3.6)	0/70 (0.0)	
Both	282/382 (73.8)	260/354 (73.4)	100/111 (87.4)	60/70 (85.7)	
None	48/382 (12.6)	54/354 (15.3)	3/111 (2.7)	4/70 (5.7)	

eTable 1: Demographic table for Erasmus MC, Haaglanden MC, UZ Leuven and Brigham Cohorts (continued)

Characteristic	EMC-Cohort (n = 382)	HMC-Cohort (n = 354)	Leuven-Cohort (n = 111)	Boston-Cohort (n = 71)	*p* value
Reasons for no combined CTx + RTx					<0.001
Due to surgical deficits	25/100 (25.0)	20/94 (21.3)	0/14 (0.0)	0/10 (0.0)	
Due to rapid progression	25/100 (25.0)	15/94 (15.6)	3/14 (21.4)	1/10 (10.0)	
Pre-op already ineligible	28/100 (28.0)	50/94 (53.2)	8/14 (57.1)	1/10 (10.0)	
Patient's wish	17/100 (17.0)	4/94 (4.3)	1/14 (7.1)	2/10 (20.0)	
Due to inclusion in clinical trial	2/100 (2.0)	0/94 (0.0)	1/14 (7.1)	4/10 (40.0)	
Unknown	3/100 (3.0)	5/94 (5.3)	0/14 (0.0)	2/10 (20.0)	
6-week NIHSS-status, pre-op as ref					
Deteriorated	117/373 (31.4)	81/323 (25.1)	27/102 (26.5)	21/55 (38.2)	0.11
New	54/117 (46.2)	25/81 (30.9)	9/27 (33.3)	6/21 (28.6)	
Worsened	63/117 (53.8)	56/81 (69.1)	18/27 (66.7)	15/21 (71.4)	
Transient	13/117 (11.1)	15/81 (18.5)	7/27 (25.9)	3/21 (14.3)	
Permanent	68/117 (58.1)	31/81 (38.3)	19/27 (70.4)	13/21 (61.9)	
Unknown	36/117 (30.8)	35/81 (43.2)	1/27 (3.7)	5/21 (23.8)	
Improved	81/373 (21.7)	114/323 (35.3)	41/102 (40.2)	22/55 (40.0)	<0.001
Stable	175/373 (46.9)	128/323 (39.6)	34/102 (33.3)	12/55 (21.8)	<0.001
3-month NIHSS-status, pre-op as ref					
Deteriorated	113/290 (39.0)	61/219 (27.9)	34/100 (34.0)	9/49 (18.4)	0.0071
New	54/113 (47.8)	29/61 (47.5)	13/34 (38.2)	4/9 (44.4)	
Worsened	59/113 (52.2)	32/61 (52.5)	21/34 (61.8)	5/9 (55.6)	
Improved	56/290 (19.3)	79/219 (50.0)	34/100 (34.0)	18/49 (36.7)	<0.001
Stable	121/290 (41.7)	79/219 (50.0)	32/100 (32.0)	22/49 (44.9)	0.22
6-month NIHSS-status, pre-op as ref					
Deteriorated	124/268 (46.3)	66/189 (34.9)	35/96 (36.5)	13/49 (26.5)	0.0065
New	64/125 (51.2)	33/66 (50.0)	13/35 (37.1)	6/13 (46.2)	
Worsened	61/125 (48.8)	33/66 (50.0)	22/35 (62.9)	7/13 (53.8)	
Improved	47/268 (17.5)	58/189 (30.7)	36/96 (37.5)	18/49 (36.7)	<0.001
Stable	97/268 (36.2)	65/189 (34.4)	25/96 (26.0)	18/49 (36.7)	0.33

eTable 1: Demographic table for Erasmus MC, Haaglanden MC, UZ Leuven and Brigham Cohorts (continued)

Characteristic	EMC-Cohort (n = 382)	HMC-Cohort (n = 354)	Leuven-Cohort (n = 111)	Boston-Cohort (n = 71)	*p* value
Postoperative vascular complications					
None	271/374 (89.0)	258/344 (90.1)	100/106 (94.3)	69/70 (98.6)	<0.001
Major ischemia	23/374 (6.1)	16/344 (4.7)	3/106 (2.8)	1/70 (1.4)	0.25
Rebleed	18/374 (4.8)	15/344 (4.4)	3/106 (2.8)	0/70 (0.0)	0.52
Preoperative CE tumor volume, ml					<0.001
Mean (SD)	59.5 (52.5)	78.5 (57.3)	32.6 (22.6)	45.9 (50.7)	
Median (Q1-Q3)	45.1 (24.3-80.8)	63.3 (35.8-119.3)	29.2 (14.3-49.8)	28.6 (11.1-67.1)	
Range	0.4-237.0	0.7-237.6	0.75-113.2	2.7-225.8	
Postoperative CE tumor volume, ml					<0.001
Mean (SD)	7.4 (14.7)	6.0 (12.2)	0.95 (3.3)	0.6 (2.0)	
Median (Q1-Q3)	2.1 (0.3-6.8)	1.8 (0-5.7.0)	2.9 (1.4-5.0)	0.0 (0.0-0.4)	
Range	0.0-94.0	0.0-93.7	0.0-26.4	0.0-14.9	
Extent of resection CE tumor, % by volume					<0.001
Mean (SD)	90.0 (12.8)	91.6 (13.6)	94.0 (9.7)	97.9 (6.8)	
Median (Q1-Q3)	94.3 (85.9-98.6)	97.1 (88.4-100.0)	97.6 (94.0-99.0)	100.0 (99.2-100.0)	
Range	8.9-100.0	9.0-100.0	54.5-100.0	48.2-100.0	
Median progression-free survival, months (IQR)	6.0 (3.0-10.0)	12.0 (4.0-25.5)	10.5 (6.0-15.75)	7.0 (5.0-12.5)	
Median overall survival, months (IQR)	11.0 (6.0-17.9)	15.5 (5.5-28.0)	16.0 (11.0-23.5)	13.0 (8.3-19.8)	

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 between the Erasmus MC, Haaglanden MC, UZ Leuven and Brigham and Women's Hospital cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

eTable 2: Summary data for glioblastoma subgroups based on age

Characteristic	<70 years old, matched (1:2)			≥ 70 years old, matched (1:4)		
	Awake craniotomy (n = 109)	Asleep resection (n = 218)	*p* value	Awake craniotomy (n = 19)	Asleep resection (n = 76)	*p* value
Gender			0.87			0.75
Male	74/109 (67.9)	146/218 (67.0)		12/19 (63.2)	45/76 (59.2)	
Female	35/109 (32.1)	72/218 (33.0)		7/19 (36.8)	31/76 (40.9)	
Age at diagnosis, years			0.56			0.78
Mean (SD)	54.2 (11.1)	56.0 (9.4)		75.2 (5.4)	74.7 (4.0)	
Median (IQR)	55.0 (48.0-64.0)	57.0 (51.3-64.0)		73.0 (70.0-78.5)	74.0 (71.0-77.3)	
Range	22.0-69.0	20.0-69.0		70.0-87.0	70.0-81.0	
Preoperative KPS			0.50			0.58
<60	1/109 (0.9)	0/218 (0.0)		0/19 (0.0)	0/76 (0.0)	
60	1/109 (0.9)	3/218 (1.4)		0/19 (0.0)	1/76 (1.3)	
70	6/109 (5.5)	19/218 (8.7)		0/19 (0.0)	3/76 (3.9)	
80	18/109 (16.5)	54/218 (24.8)		7/19 (36.8)	19/76 (25.0)	
90	54/109 (49.5)	100/218 (45.9)		8/19 (42.1)	39/76 (51.3)	
100	29/109 (26.6)	42/218 (19.3)		4/19 (21.1)	14/76 (18.4)	
Median preoperative KPS (IQR)	90 (90-100)	90 (90-90)		90 (80-90)	90 (80-90)	
Preoperative ASA score			0.015			0.036
I	16/97 (16.5)	34/218 (15.6)		0/16 (0.0)	4/75 (5.3)	
II	52/97 (53.6)	150/218 (68.8)		6/16 (37.5)	52/75 (69.0)	
III	29/97 (29.9)	32/218 (14.7)		10/16 (62.5)	19/75 (25.3)	
IV	0/97 (0.0)	2/218 (0.9)		0/16 (0.0)	0/75 (0.0)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-2)		3 (3-3)	2 (2-3)	

eTable 2: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:2)			≥ 70 years old, matched (1:4)		
	Awake craniotomy (n = 109)	Asleep resection (n = 218)	*p* value	Awake craniotomy (n = 19)	Asleep resection (n = 76)	*p* value
Preoperative NIHSS score			0.39			0.76
0	57/109 (52.3)	96/218 (44.0)		5/19 (26.3)	31/76 (40.8)	
1	32/109 (29.4)	70/218 (32.1)		9/19 (47.3)	19/76 (25.0)	
2	11/109 (10.1)	33/218 (15.1)		4/19 (21.1)	16/76 (21.1)	
3	2/109 (1.8)	10/218 (4.6)		1/19 (5.3)	5/76 (6.6)	
4	4/109 (3.7)	3/218 (1.4)		0/19 (0.0)	4/76 (5.3)	
>4	3/109 (2.8)	6/218 (2.8)		0/19 (0.0)	1/76 (1.3)	
Median preoperative NIHSS score (IQR)	0 (0-1)	0 (0-1)		1 (1-2)	1 (0-2)	
Tumor location by lobe			0.57			<0.001
Frontal	45/109 (41.3)	84/218 (38.5)		6/19 (31.6)	29/76 (38.2)	
Parietal	29/109 (26.6)	53/218 (24.3)		3/19 (15.8)	19/76 (25.0)	
Temporal	34/109 (31.2)	74/218 (33.9)		10/19 (52.6)	21/76 (27.6)	
Occipital	1/109 (0.9)	7/218 (3.2)		0/19 (0.0)	7/76 (9.2)	
Insula	0/109 (0.0)	0/218 (0.0)		0/19 (0.0)	0/76 (0.0)	
Tumor location by hemisphere			0.34			1.000
Left	89/109 (81.7)	168/218 (77.1)		13/19 (68.4)	52/76 (68.4)	
Right	20/109 (18.3)	50/218 (22.9)		6/19 (31.6)	24/76 (31.6)	
Tumor location by eloquence			0.0026			0.37
Motor	51/109 (46.8)	100/218 (45.9)		8/19 (42.1)	45/76 (59.2)	
Sensory	7/109 (6.4)	11/218 (5.0)		2/19 (10.5)	3/76 (3.9)	
Language	69/109 (63.3)	124/218 (56.9)		11/19 (57.9)	40/76 (52.6)	
Visual	2/109 (1.8)	36/218 (16.5)		0/19 (0.0)	11/76 (14.5)	
IDH status			0.19			0.51
Wildtype	82/89 (92.1)	127/132 (96.2)		17/17 (100.0)	43/44 (97.7)	
Mutant	7/89 (12.4)	5/132 (3.8)		0/17 (0.0)	1/44 (2.3)	
MGMT status			0.0016			0.62
Methylated	35/68 (51.5)	35/123 (28.5)		6/16 (37.5)	24/54 (44.4)	
Unmethylated	33/68 (48.5)	88/123 (71.5)		10/16 (62.5)	30/54 (55.6)	

eTable 2: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:2)			≥ 70 years old, matched (1:4)		
	Awake craniotomy (n = 109)	Asleep resection (n = 218)	*p* value	Awake craniotomy (n = 19)	Asleep resection (n = 76)	*p* value
Surgical adjuncts						
Intraoperative ultrasound	21/109 (19.3)	25/218 (11.5)	0.056	7/19 (36.8)	5/76 (6.6)	<0.001
Intraoperative fluorescence	26/109 (23.9)	53/218 (24.3)	0.93	3/19 (15.8)	17/76 (22.4)	0.53
Postoperative adjuvant therapy			0.12			0.54
Radiotherapy only	1/109 (0.9)	8/218 (3.7)		2/19 (10.5)	6/76 (7.9)	
Chemotherapy only	3/109 (2.8)	1/218 (0.5)		0/19 (0.0)	0/76 (0.0)	
Chemoradiotherapy	102/109 (93.6)	199/218 (91.3)		17/19 (89.5)	69/76 (90.8)	
None	3/109 (2.8)	10/218 (4.6)		0/19 (0.)	1/76 (1.3)	
Reasons for no combined CTx + RTx			0.82			NA
Due to surgical deficits	0/7 (0.0)	7/19 (36.8)		0/2 (0.0)	1/7 (14.3)	
Due to rapid progression	2/7 (28.6)	4/19 (21.1)		0/2 (0.0)	1/7 (14.3)	
Pre-op already ineligible	2/7 (28.6)	5/19 (26.3)		2/2 (100.0)	3/7 (42.9)	
Patient's wish	1/7 (14.3)	3/19 (15.8)		0/2 (0.0)	1/7 (14.3)	
Due to inclusion in clinical trial	1/7 (14.3)	0/19 (0.0)		0/2 (0.)	1/7 (14.3)	
Unknown	0/7 (0.0)	0/19 (0.0)		0/2 (0.0)	0/7 (0.0)	
6-week NIHSS-status, pre-op as ref						
Deteriorated	18/104 (17.3)	58/209 (28.2)	0.035	1/17 (5.8)	21/72 (29.2)	0.046
New	11/18 (61.1)	30/58 (51.7)		0/1 (0.0)	8/21 (38.1)	
Worsened	7/18 (38.9)	28/58 (48.3)		1/1 (100.0)	13/21 (61.9)	
Transient	6/18 (33.3)	10/58 (15.5)		0/1 (0.0)	3/21 (14.3)	
Permanent	12/18 (66.7)	38/58 (65.5)		1/1 (100.0)	15/21 (71.4)	
Unknown	0/18 (0.0)	10/58 (17.2)		0/1 (0.0)	3/21 (14.3)	
Improved	29/104 (27.9)	59/209 (28.2)	0.96	8/17 (47.1)	14/72 (19.4)	0.018
Stable	57/104 (54.8)	95/209 (45.5)	0.12	8/17 (47.1)	37/72 (51.4)	0.75
6-week KPS status, pre-op as ref						
Deteriorated	32/105 (30.5)	79/213 (37.1)	0.25	10/17 (58.8)	38/74 (51.4)	0.58
Improved	22/105 (21.0)	49/213 (23.0)	0.69	4/17 (23.5)	10/74 (13.5)	0.31
Stable	50/105 (47.6)	85/213 (40.0)	0.20	3/17 (17.6)	26/74 (35.1)	0.16

eTable 2: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:2)			≥ 70 years old, matched (1:4)		
	Awake craniotomy (n = 109)	Asleep resection (n = 218)	*p* value	Awake craniotomy (n = 19)	Asleep resection (n = 76)	*p* value
3-month NIHSS-status, pre-op as ref						
Deteriorated	22/100 (22.0)	60/190 (31.6)	0.085	3/16 (18.8)	24/64 (37.5)	0.16
New	13/22 (59.1)	33/60 (55.0)		0/3 (0.0)	12/24 (50.0)	
Worsened	9/22 (40.9)	27/60 (45.0)		3/3 (100.0)	12/24 (50.0)	
Improved	29/100 (29.0)	51/190 (26.8)	0.69	7/16 (43.8)	14/64 (25.0)	0.14
Stable	49/100 (49.0)	79/190 (41.6)	0.23	6/16 (37.5)	26/64 (40.6)	0.82
3-month KPS status, pre-op as ref						
Deteriorated	38/100 (38.0)	82/195 (42.1)	0.50	8/16 (50.0)	34/64 (53.1)	0.83
Improved	18/100 (18.0)	44/195 (22.6)	0.36	2/16 (12.5)	8/64 (12.5)	1.000
Stable	44/100 (44.0)	69/195 (35.4)	0.15	6/16 (37.5)	22/64 (34.4)	0.82
6-month NIHSS-status, pre-op as ref						
Deteriorated	24/99 (24.2)	71/185 (38.4)	0.016	6/14 (42.9)	26/55 (47.3)	0.77
New	17/24 (70.8)	40/71 (56.3)		0/6 (0.0)	16/26 (61.5)	
Worsened	7/24 (29.2)	31/71 (43.7)		6/6 (100.0)	10/26 (38.5)	
Improved	28/99 (28.3)	52/185 (28.1)	0.97	4/14 (28.6)	10/55 (18.2)	0.39
Stable	47/99 (47.5)	62/185 (33.5)	0.021	4/14 (28.6)	19/55 (34.5)	0.68
6-month KPS status, pre-op as ref						
Deteriorated	41/100 (41.0)	90/185 (48.6)	0.22	8/14 (57.1)	34/56 (60.7)	0.81
Improved	18/101 (18.0)	38/185 (20.5)	0.61	0/14 (0.0)	7/56 (12.5)	0.17
Stable	41/100 (41.0)	57/185 (30.8)	0.084	6/14 (42.9)	15/56 (26.8)	0.24
Postoperative vascular complications			0.29			0.98
None	106/109 (97.2)	199/214 (93.0)		19/19 (100.0)	68/71 (95.8)	
Major ischemia	2/109 (1.8)	10/214 (4.7)		0/19 (0.0)	2/71 (2.8)	
Rebleed	1/109 (0.9)	5/214 (2.3)		0/19 (0.0)	2/71 (2.8)	
Preoperative CE tumor volume, ml			0.14			0.58
Mean (SD)	39.4 (48.0)	46.6 (36.4)		31.3 (40.2)	35.6 (26.7)	
Median (Q1-Q3)	24.2 (12.2-51.0)	36.5 (18.4-60.9)		17.3 (9.0-34.2)	27.4 (17.5-53.6)	
Range	0.8-225.8	1.7-197.0		2.7-160.1	0.4-123.9	

eTable 2: Summary data for glioblastoma subgroups based on age (continued)

Characteristic	<70 years old, matched (1:2)			≥ 70 years old, matched (1:4)		
	Awake craniotomy (n = 109)	Asleep resection (n = 218)	*p* value	Awake craniotomy (n = 19)	Asleep resection (n = 76)	*p* value
Postoperative CE tumor volume, ml			0.0039			0.037
Mean (SD)	2.1 (6.1)	5.9 (12.6)		0.4 (7.6)	3.7 (6.5)	
Median (Q1-Q3)	0.1 (0.0-1.5)	1.5 (0.0-5.6)		0.0 (0.0-0.3)	1.0 (0.0-4.9)	
Range	0.0-41.0	0.0-81.7		0.0-2.4	0.0-36.0	
Extent of resection CE tumor, % by volume			<0.001			0.0032
Mean (SD)	95.1 (8.8)	86.6 (19.2)		98.1 (3.7)	86.2 (19.7)	
Median (Q1-Q3)	99.7 (93.5-100.0)	95.2 (82.0-100.0)		100.0 (98.7-100.0)	94.0 (80.1-100.0)	
Range	48.2-100.0	17.6.-100.0		87.5-100.0	12.7-100.0	
Median progression-free survival, months (IQR)	11.0 (9.0-13.0)	10.0 (8.0-11.0)	0.22	8.0 (6.0-11.0)	9.0 (7.0-11.0)	0.86
Median overall survival, months (IQR)	24.0 (18.0-39.0)	20.5 (18.0-22.5)	0.031	12.0 (11.0-NA)	15.5 (12.5-22.0)	0.87

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the matched age cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

eTable 3: Summary data for glioblastoma subgroups based on preoperative NIHSS score

Characteristic	NIHSS score 0-1, matched (1:2)			NIHSS score ≥ 2, matched (1:4)		
	Awake craniotomy (n = 103)	Asleep resection (n = 206)	*p* value	Awake craniotomy (n = 25)	Asleep resection (n = 100)	*p* value
Gender			0.55			0.47
Male	72/103 (70.0)	137/206 (66.5)		16/25 (64.0)	56/100 (56.0)	
Female	31/103 (30.1)	69/206 (33.5)		9/25 (36.0)	44/100 (44.0)	
Age at diagnosis, years			0.061			0.78
Mean (SD)	56.3 (12.9)	59.2 (11.5)		61.9 (12.0)	62.5 (10.2)	
Median (IQR)	56.0 (49.0-66.0)	59.5 (52.0-68.0)		65.0 (55.0-69.0)	65.0 (56.5-70.0)	
Range	22.0-87.0	23.0-81.0		34.0-82.0	20.0-79.0	
Preoperative KPS			0.94			0.71
<60	0/103 (0.0)	0/206 (0.0)		1/25 (4.0)	0/100 (0.0)	
60	1/103 (1.0)	1/206 (0.5)		0/25 (0.0)	7/100 (7.0)	
70	3/103 (2.9)	8/206 (3.9)		3/25 (12.0)	19/100 (19.0)	
80	13/103 (12.6)	25/206 (12.1)		12/25 (48.0)	42/100 (42.0)	
90	54/103 (52.4)	117/206 (56.8)		8/25 (32.0)	30/100 (30.0)	
100	32/103 (31.1)	55/206 (26.7)		1/25 (4.0)	2/100 (2.0)	
Median preoperative KPS (IQR)	90 (90-100)	90 (90-100)		80 (80-90)	80 (70-90)	
Preoperative ASA score			0.0071			0.21
I	13/92 (14.1)	32/206 (15.5)		3/21 (14.3)	8/99 (8.1)	
II	47/92 (51.1)	139/206 (67.5)		11/21 (52.4)	71/99 (71.7)	
III	32/92 (34.8)	35/206 (17.0)		7/21 (33.3)	19/99 (19.2)	
IV	0/92 (0.0)	0/206 (0.0)		0/21 (0.0)	1/99 (1.0)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-2)		2 (2-3)	2 (2-2)	

eTable 3: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:2)			NIHSS score ≥ 2, matched (1:4)		
	Awake craniotomy (n = 103)	Asleep resection (n = 206)	*p* value	Awake craniotomy (n = 25)	Asleep resection (n = 100)	*p* value
Preoperative NIHSS score			0.62			0.66
0	62/103 (60.2)	118/206 (8.7)		0/25 (0.0)	0/100 (0.0)	
1	41/103 (39.8)	88/206 (42.7)		0/25 (0.0)	0/100 (0.0)	
2	0/103 (0.0)	0/206 (0.0)		15/25 (60.0)	56/100 (56.0)	
3	0/103 (0.0)	0/206 (0.0)		3/25 (12.0)	17/100 (17.0)	
4	0/103 (0.0)	0/206 (0.0)		4/25 (16.0)	10/100 (10.0)	
>4	0/103 (0.0)	0/206 (0.0)		3/25 (12.0)	17/100 (17.0)	
Median preoperative NIHSS score (IQR)	0 (0-1)	0 (0-1)		2 (2-4)	2 (2-4)	
Tumor location by lobe			0.60			0.85
Frontal	40/103 (38.8)	70/206 (34.0)		11/25 (44.0)	43/100 (43.0)	
Parietal	25/103 (24.3)	53/206 (25.7)		7/25 (28.0)	33/100 (33.0)	
Temporal	37/103 (35.9)	75/206 (36.4)		7/25 (28.0)	25/100 (25.0)	
Occipital	1/103 (1.0)	8/206 (3.9)		0/25 (0.0)	9/100 (9.0)	
Insula	0/103 (0.0)	0/206 (0.0)		0/25 (0.0)	0/100 (0.0)	
Tumor location by hemisphere			0.24			0.31
Left	80/103 (77.7)	147/206 (71.4)		22/25 (88.0)	79/100 (79.0)	
Right	23/103 (22.3)	59/206 (28.6)		3/25 (12.0)	21/100 (21.0)	
Tumor location by eloquence			0.019			0.021
Motor	47/103 (45.6)	97/206 (47.1)		12/25 (48.0)	63/100 (63.0)	
Sensory	6/103 (5.8)	14/206 (6.8)		3/25 (12.0)	4/100 (4.0)	
Language	62/103 (60.2)	112/206 (54.4)		18/25 (72.0)	50/100 (50.0)	
Visual	2/103 (1.9)	28/206 (13.6)		0/25 (0.0)	27/100 (27.0)	
IDH status			0.24			0.37
Wildtype	81/89 (91.0)	116/122 (95.1)		17/17 (100.0)	58/59 (98.3)	
Mutant	8/89 (9.0)	6/122 (4.9)		0/17 (0.0)	1/59 (1.7)	
MGMT status			0.13			0.033
Methylated	31/68 (45.6)	46/133 (34.6)		10/16 (62.5)	17/52 (32.6)	
Unmethylated	37/68 (54.4)	87/133 (65.4)		6/16 (37.5)	35/52 (67.3)	

eTable 3: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:2)			NIHSS score ≥ 2, matched (1:4)		
	Awake craniotomy (n = 103)	Asleep resection (n = 206)	*p* value	Awake craniotomy (n = 25)	Asleep resection (n = 100)	*p* value
Surgical adjuncts						0.85
Intraoperative ultrasound	24/103 (23.3)	19/206 (9.2)	<0.001	4/25 (16.0)	14/100 (14.0)	
Intraoperative fluorescence	21/103 (20.4)	41/206 (20.0)	0.93	8/25 (32.0)	32/100 (32.0)	
Postoperative adjuvant therapy			0.21			0.54
Radiotherapy only	3/103 (2.9)	11/206 (5.3)		0/25 (0.0)	0/100 (0.0)	
Chemotherapy only	3/103 (2.9)	0/206 (0.0)		0/25 (0.0)	0/100 (0.0)	
Chemoradiotherapy	95/103 (92.2)	188/206 (91.3)		24/25 (96.0)	97/100 (97.0)	
None	2/103 (2.9)	7/206 (3.4)		1/25 (4.0)	3/100 (3.0)	
Reasons for no combined CTx + RTx			0.66			NA
Due to surgical deficits	0/8 (0.0)	5/18 (27.8)		0/1 (0.0)	1/3 (33.3)	
Due to rapid progression	2/8 (25.0)	4/18 (22.2)		0/1 (0.0)	1/3 (33.3)	
Pre-op already ineligible	4/8 (50.0)	4/18 (22.2)		0/1 (0.0)	0.3 (0.0)	
Patient's wish	1/8 (12.5)	4/18 (22.2)		0/1 (0.0)	1/3 (0.0)	
Due to inclusion in clinical trial	1/8 (12.5)	1/18 (22.2)		0/1 (0.0)	0/3 (0.0)	
Unknown	0/8 (0.0)	0/18 (0.0)		1/1 (100.0)	0.3 (0.0)	
6-week NIHSS-status, pre-op as ref						
Deteriorated	19/96 (19.8)	64/199 (32.2)	0.027	3/23 (13.0)	16/96 (16.7)	0.67
New	11/19 (57.9)	42/624(65.6)		0/3 (0.0)	0/16 (0.0)	
Worsened	8/19 (42.1)	22/64 (34.4)		3/3 (100.0)	16/16 (100.0)	
Transient	4/19 (21.1)	11/64 (17.2)		0/3 (0.0)	1/16 (6.3)	
Permanent	13/19 (68.4)	43/64 (67.2)		3/3 (100.0)	12/16 (75.0)	
Unknown	2/19 (10.5)	10/64 (15.6)		0/3 (0.0)	3/16 (18.8)	
Improved	22/96 (22.9)	29/199 (14.6)	0.078	15/23 (65.2)	54/96 (56.3)	0.44
Stable	55/96 (57.3)	106/199 (53.3)	0.52	5/23 (21.7)	26/96 (27.1)	0.60
6-week KPS status, pre-op as ref						
Deteriorated	34/98 (34.7)	89/202 (44.1)	0.12	9/24 (37.5)	31/98 (31.6)	0.58
Improved	20/98 (20.4)	22/202 (10.9)	0.026	6/24 (25.0)	38/98 (38.8)	0.20
Stable	42/98 (42.9)	91/202 (45.0)	0.91	9/24 (37.5)	29/98 (29.6)	0.49

eTable 3: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:2)			NIHSS score ≥ 2, matched (1:4)		
	Awake craniotomy (n = 103)	Asleep resection (n = 206)	*p* value	Awake craniotomy (n = 25)	Asleep resection (n = 100)	*p* value
3-month NIHSS-status, pre-op as ref						
Deteriorated	22/93 (23.7)	67/178 (37.6)	0.021	3/23 (13.0)	25/89 (28.1)	0.14
New	13/22 (59.1)	44/67 (65.7)		0/3 (0.0)	0/25 (0.0)	
Worsened	9/22 (40.9)	23/67 (34.4)		3/3 (100.0)	25/25 (100.0)	
Improved	20/93 (21.5)	27/178 (15.2)	0.19	14/23 (60.9)	46/89 (51.7)	0.43
Stable	51/93 (54.8)	84/178 (47.2)	0.24	6/23 (26.1)	18/89 (20.2)	0.54
3-month KPS status, pre-op as ref						
Deteriorated	37/93 (39.8)	92/179 (51.4)	0.070	9/23 (39.1)	29/92 (31.5)	0.49
Improved	15/93 (16.1)	19/179 (10.6)	0.19	5/23 (21.7)	35/92 (38.0)	0.14
Stable	41/93 (44.1)	68/179 (38.0)	0.33	9/23 (39.1)	18/92 (19.6)	0.050
6-month NIHSS-status, pre-op as ref						
Deteriorated	27/93 (29.0)	79/167 (47.3)	0.0041	3/20 (15.0)	27/81 (33.3)	0.11
New	16/27 (59.3)	55/79 (69.6)		0/3 (0.0)	0/81 (0.0)	
Worsened	11/27 (40.7)	24/79 (30.4)		3/3 (100.0)	81/1 (100.0)	
Improved	19/93 (20.4)	27/167 (16.2)	0.40	13/20 (65.0)	37/81 (45.7)	0.12
Stable	47/93 (50.5)	61/167 (36.5)	0.028	4/20 (20.0)	17/81 (21.0)	0.92
6-month KPS status, pre-op as ref						
Deteriorated	43/96 (44.8)	92/167 (55.1)	0.11	7/20 (35.0)	33/81 (40.7)	0.64
Improved	13/96 (13.5)	16/167 (9.6)	0.33	5/20 (25.0)	28/81 (34.6)	0.42
Stable	40/96 (41.7)	59/167 (35.3)	0.30	8/20 (40.0)	20/81 (24.7)	0.17
Postoperative vascular complications			0.69			0.59
None	98/101 (97.0)	197/206 (95.6)		25/25 (100.0)	96/100 (96.0)	
Major ischemia	2/101 (2.0)	4/206 (1.9)		0/25 (0.0)	3/100 (3.0)	
Rebleed	1/101 (1.0)	5/206 (2.4)		0/25 (0.0)	1/100 (1.0)	
Preoperative CE tumor volume, ml			0.48			0.13
Mean (SD)	38.8 (49.5)	42.2 (33.5)		36.0 (34.5)	47.1 (32.0)	
Median (Q1-Q3)	21.7 (10.5-49.6)	34.2 (16.7-56.4)		26.9 (18.2-36.1)	38.5 (23.5-63.9)	
Range	0.8-225.8	0.4-180.5		3.9-160.0	0.8-147.6	

eTable 3: Summary data for glioblastoma subgroups based on preoperative NIHSS score (continued)

Characteristic	NIHSS score 0-1, matched (1:2)			NIHSS score ≥ 2, matched (1:4)		
	Awake craniotomy (n = 103)	Asleep resection (n = 206)	*p* value	Awake craniotomy (n = 25)	Asleep resection (n = 100)	*p* value
Postoperative CE tumor volume, ml			0.0056			0.048
Mean (SD)	2.1 (6.3)	5.6 (11.6)		1.2 (2.0)	4.3 (7.7)	
Median (Q1-Q3)	0.0 (0.0-1.1)	1.7 (0.0-5.6)		0.06 (0.0-1.7)	0.9 (0.0-5.1)	
Range	0.0-41.0	0.0-81.7		0.0-9.2	0.0-51.6	
Extent of resection CE tumor, % by volume			<0.001			0.13
Mean (SD)	95.6 (8.5)	86.0 (19.3)		94.9 (7.3)	88.5 (17.0)	
Median (Q1-Q3)	99.9 (95.7-100.0)	93.9 (81.7-100.0)		96.9 (92.8-100.0)	97.9 (82.8-100.0)	
Range	48.2-100.0	9.0-100.0		71.4-100.0	12.7-100.0	
Median progression-free survival, months (IQR)	10.8 (9.0-13.0)	10.8 (9.0-12.0)	0.30	6.5 (4.5-25.0)	7.5 (6.0-10.0)	0.99
Median overall survival, months (IQR)	20.0 (17.0-39.0)	22.0 (19.5-24.0)	0.17	15.5 (10.0-55.0)	18.0 (15.5-21.0)	0.84

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the unmatched and matched NIHSS cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

eTable 4: Summary data for glioblastoma subgroups based on preoperative KPS

Characteristic	KPS 90-100, matched (1:2)			KPS ≤ 80, matched (1:4)		
	Awake craniotomy (n = 95)	Asleep resection (n = 190)	p value	Awake craniotomy (n = 33)	Asleep resection (n = 132)	p value
Gender						0.58
Male	69/95 (72.6)	138/190 (72.6)		17/33 (51.5)	75/132 (56.8)	
Female	26/95 (27.4)	52/190 (27.4)	1.000	16/33 (48.5)	57/132 (43.2)	
Age at diagnosis, years			0.088			0.97
Mean (SD)	56.2 (12.8)	58.8 (11.7)		60.8 (12.8)	60.8 (9.9)	
Median (IQR)	57.0 (48.0-66.0)	59.5 (52.0-66.8)		61.0 (54.0-69.0)	61.5 (54.0-70.0)	
Range	22.0-86.0	20.0-81.0		34.0-87.0	25.0-79.0	
Preoperative KPS			0.75			0.59
<60	0/95 (0.0)	0/190 (0.0)		1/33 (3.0)	0/132 (0.0)	
60	0/95 (0.0)	0/190 (0.0)		1/33 (3.0)	7/132 (5.3)	
70	0/95 (0.0)	0/190 (0.0)		6/33 (18.2)	30/132 (22.7)	
80	0/95 (0.0)	0/190 (0.0)		25/33 (75.8)	95/132 (72.0)	
90	62/95 (65.3)	136/190 (71.6)		0/33 (0.0)	0/132 (0.0)	
100	33/95 (34.7)	54/190 (28.4)		0/33 (0.0)	0/132 (0.0)	
Median preoperative KPS (IQR)	90 (90-100)	90 (90-100)		80 (80-80)	80 (70-80)	
Preoperative ASA score			0.054			0.18
I	14/88 (15.9)	30/189 (15.9)		2/25 (8.0)	15/132 (11.4)	
II	44/88 (50.0)	122/189 (64.6)		14/25 (56.0)	92/132 (69.7)	
III	30/88 (34.1)	37/189 (19.6)		9/25 (36.0)	23/132 (17.4)	
IV	0/88 (0.0)	0/189 (0.0)		0/25 (0.0)	2/132 (1.5)	
Median preoperative ASA score (IQR)	2 (2-3)	2 (2-2)		2 (2-3)	2 (2-2)	

eTable 4: Summary data for glioblastoma subgroups based on preoperative KPS (continued)

Characteristic	KPS 90-100, matched (1:2)			KPS ≤ 80, matched (1:4)		
	Awake craniotomy (n = 95)	Asleep resection (n = 190)	p value	Awake craniotomy (n = 33)	Asleep resection (n = 132)	p value
Preoperative NIHSS score			0.15			0.72
0	59/95 (62.1)	107/190 (56.3)		3/33 (9.1)	28/132 (21.2)	
1	28/95 (29.5)	58/190 (30.5)		14/33 (42.4)	39/132 (29.5)	
2	5/95 (5.3)	23/190 (12.1)		10/33 (30.3)	32/132 (24.2)	
3	1/95 (1.1)	1/190 (0.5)		2/33 (6.1)	15/132 (11.4)	
4	3/95 (3.2)	0/190 (0.0)		1/33 (3.0)	7/132 (5.3)	
>4	0/95 (0.0)	1/190 (0.5)		3/33 (9.1)	11/132 (8.3)	
Median preoperative NIHSS score (IQR)	0 (0-1)	0 (0-1)		1 (1-2)	1 (1-2)	
Tumor location by lobe			0.37			0.75
Frontal	37/95 (38.9)	59/190 (31.1)		14/33 (42.4)	52/132 (39.4)	
Parietal	23/95 (24.2)	54/190 (28.4)		9/33 (27.3)	26/132 (19.7)	
Temporal	34/95 (35.8)	68/190 (35.8)		10/33 (30.3)	47/132 (35.6)	
Occipital	1/95 (1.1)	9/190 (4.7)		0/33 (0.0)	7/132 (5.3)	
Insula	0/95 (0.0)	0/190 (0.0)		0/33 (0.0)	0/132 (0.0)	
Tumor location by hemisphere			0.18			1.000
Left	75/95 (78.9)	136/190 (71.6)		27/33 (81.8)	108/132 (81.8)	
Right	20/95 (21.1)	54/190 (38.4)		6/33 (18.2)	24/132 (18.2)	
Tumor location by eloquence			0.0096			0.086
Motor	46/95 (48.4)	96/190 (50.5)		13/33 (39.4)	67/132 (50.8)	
Sensory	7/95 (7.4)	11/190 (5.8)		2/33 (6.1)	3/132 (2.3)	
Language	55/95 (57.9)	101/190 (53.2)		25/33 (75.8)	82/132 (62.1)	
Visual	2/95 (2.1)	31/190 (16.3)		0/33 (0.0)	23/132 (17.4)	
IDH status			0.15			0.46
Wildtype	75/82 (91.5)	106/110 (96.4)		24/24 (100.0)	66/67 (98.5)	
Mutant	7/82 (8.5)	4/110 (3.6)		0/24 (0.0)	1/67 (1.5)	
MGMT status			0.24			0.0056
Methylated	26/63 (41.3)	39/120 (31.5)		15/21 (71.4)	26/70 (37.1)	
Unmethylated	37/63 (58.7)	81/120 (67.5)		6/21 (28.6)	44/70 (62.9)	

eTable 4: Summary data for glioblastoma subgroups based on preoperative KPS (continued)

Characteristic	KPS 90-100, matched (1:2)			KPS ≤ 80, matched (1:4)		
	Awake craniotomy (n = 95)	Asleep resection (n = 190)	p value	Awake craniotomy (n = 33)	Asleep resection (n = 132)	p value
Surgical adjuncts						0.73
Intraoperative ultrasound	21/95 (22.1)	14/190 (7.4)	<0.001	7/33 (21.2)	20/132 (15.2)	
Intraoperative fluorescence	24/95 (25.3)	43/190 (22.6)	0.61	5/33 (15.2)	18/132 (13.6)	
Postoperative adjuvant therapy			0.25			0.49
Radiotherapy only	3/95 (3.2)	8/190 (4.2)		0/33 (0.0)	0/132 (0.0)	
Chemotherapy only	3/95 (3.2)	0/190 (0.0)		0/33 (0.0)	0/132 (0.0)	
Chemoradiotherapy	88/95 (92.6)	177/190 (93.2)		31/33 (93.9)	120/132 (90.1)	
None	1/95 (1.1)	5/190 (2.6)		2/33 (6.1)	12/132 (9.1)	
Reasons for no combined CTx + RTx			0.70			NA
Due to surgical deficits	0/7 (0.0)	3/13 (23.1)		0/2 (0.0)	5/12 (41.7)	
Due to rapid progression	1/7 (14.3)	2/13 (15.4)		1/2 (50.0)	4/12 (33.3)	
Pre-op already ineligible	4/7 (57.1)	3/13 (23.1)		0/2 (0.0)	0/12 (0.0)	
Patient's wish	1/7 (14.3)	4/13 (30.8)		0/2 (0.0)	3/12 (25.0)	
Due to inclusion in clinical trial	1/7 (14.3)	1/13 (7.7)		0/2 (0.0)	0/12 (0.0)	
Unknown	0/7 (0.0)	0/13 (0.0)		1/2 (50.0)	0/12 (0.0)	
6-week NIHSS-status, pre-op as ref						
Deteriorated	15/88 (17.0)	53/182 (29.1)	0.032	7/31 (22.6)	31/128 (24.2)	0.85
New	10/15 (66.7)	32/53 (60.4)		1/7 (14.3)	11/31 (35.5)	
Worsened	5/15 (33.3)	21/53 (39.6)		6/7 (85.7)	20/31 (64.5)	
Transient	4/15 (26.7)	7/53 (13.2)		1/7 (14.3)	5/31 (16.1)	
Permanent	11/15 (73.3)	38/53 (71.7)		4/7 (57.1)	22/31 (71.0)	
Unknown	0/15 (0.0)	8/53 (15.1)		2/7 (28.6)	4/31 (12.9)	
Improved	16/88 (18.2)	25/182 (13.7)	0.33	15/31 (48.4)	55/128 (43.0)	0.59
Stable	57/88 (64.8)	104/182 (57.1)	0.23	9/31 (29.0)	42/128 (32.8)	0.69
6-week KPS status, pre-op as ref						
Deteriorated	34/91 (37.4)	85/185 (45.9)	0.18	8/31 (25.8)	24/129 (18.6)	0.37
Improved	16/91 (17.6)	16/185 (8.6)	0.028	11/31 (35.5)	65/129 (50.4)	0.14
Stable	41/91 (45.1)	84/185 (45.4)	0.96	12/31 (40.0)	40/129 (31.0)	0.34

eTable 4: Summary data for glioblastoma subgroups based on preoperative KPS (continued)

Characteristic	KPS 90-100, matched (1:2)			KPS ≤ 80, matched (1:4)		
	Awake craniotomy (n = 95)	Asleep resection (n = 190)	p value	Awake craniotomy (n = 33)	Asleep resection (n = 132)	p value
3-month NIHSS-status, pre-op as ref						
Deteriorated	18/87 (20.7)	54/163 (33.1)	0.039	7/29 (24.1)	37/117 (31.6)	0.50
New	13/18 (72.2)	36/54 (66.7)		0/7 (0.0)	12/37 (32.4)	
Worsened	5/18 (27.8)	18/54 (33.3)		7/7 (100.0)	25/37 (67.6)	
Improved	19/87 (21.8)	27/163 (16.6)	0.31	15/29 (51.7)	49/117 (41.9)	0.42
Stable	50/87 (57.5)	82/163 (50.3)	0.28	7/29 (24.1)	31/117 (26.5)	0.82
3-month KPS status, pre-op as ref						
Deteriorated	38/87 (43.7)	89/163 (54.6)	0.10	8/29 (27.6)	24/120 (20.0)	0.37
Improved	10/87 (11.5)	14/163 (8.6)	0.46	10/29 (34.5)	59/120 (49.2)	0.16
Stable	39/87 (44.8)	60/163 (36.8)	0.22	11/29 (37.9)	37/120 (30.8)	0.46
6-month NIHSS-status, pre-op as ref						
Deteriorated	24/86 (27.9)	69/157 (43.9)	0.0022	6/27 (22.2)	50/109 (45.9)	0.026
New	16/24 (66.7)	45/69 (65.2)		0/6 (0.0)	17/50 (34.0)	
Worsened	8/24 (33.3)	24/69 (34.8)		6/6 (100.0)	33/50 (66.0)	
Improved	18/86 (20.9)	26/157 (16.6)	0.41	14/27 (51.9)	33/109 (30.3)	0.035
Stable	44/86 (51.2)	62/157 (39.5)	0.079	7/27 (25.9)	26/109 (23.9)	0.83
6-month KPS status, pre-op as ref						
Deteriorated	43/87 (49.4)	96/157 (61.1)	0.078	7/28 (25.0)	28/109 (25.7)	0.94
Improved	9/87 (10.3)	11/157 (7.0)	0.37	9/28 (32.1)	46/109 (42.2)	0.33
Stable	35/87 (40.2)	50/157 (31.8)	0.19	12/28 (42.9)	35/109 (32.1)	0.28
Postoperative vascular complications			0.55			0.90
None	93/95 (97.9)	181/190 (95.3)		32/33 (97.0)	123/132 (93.2)	
Major ischemia	1/95 (1.1)	5/190 (2.6)		1/33 (3.0)	6/132 (4.5)	
Rebleed	1/95 (1.1)	4/190 (2.1)		0/33 (0.0)	3/132 (2.3)	
Preoperative CE tumor volume, ml			0.44			0.40
Mean (SD)	36.3 (47.9)	40.0 (32.9)		43.8 (43.7)	49.7 (33.7)	
Median (Q1-Q3)	18.9 (10.3-43.4)	32.1 (16.8-51.8)		28.8 (16.2-55.4)	40.3 (25.0-67.7)	
Range	0.8-241.2	0.4-197.0		2.7-208.0	0.8-153.8	

eTable 4: Summary data for glioblastoma subgroups based on preoperative KPS (continued)

Characteristic	KPS 90-100, matched (1:2)			KPS ≤ 80, matched (1:4)		
	Awake craniotomy (n = 95)	Asleep resection (n = 190)	p value	Awake craniotomy (n = 33)	Asleep resection (n = 132)	p value
Postoperative CE tumor volume, ml			0.0026			0.046
Mean (SD)	1.5 (4.9)	4.8 (9.7)		2.9 (7.4)	7.9 (13.6)	
Median (Q1-Q3)	0.0 (0.0-1.0)	1.4 (0.0-5.0)		0.3 (0.0-2.6)	2.3 (0.3-8.5)	
Range	0.0-41.0	0.0-72.7		0.0-40.0	0.0-81.7	
Extent of resection CE tumor, % by volume			<0.001			0.018
Mean (SD)	96.2 (6.6)	86.0 (18.7)		93.7 (11.6)	83.6 (21.5)	
Median (Q1-Q3)	100.0 (95.7-100.0)	94.3 (80.8-100.0)		98.7 (92.4-100.0)	92.3 (79.3-98.6)	
Range	71.1-100.0	9.0-100.0		48.2-100.0	12.7-100.0	
Median progression-free survival, months (IQR)	11.0 (9.5-14.0)	10.5 (8.5-12.5)	0.24	7.0 (5.0-10.0)	9.0 (7.0-10.5)	0.60
Median overall survival, months (IQR)	24.0 (17.0-39.0)	20.0 (18.0-23.0)	0.11	12.0 (9.0-43.5)	18.5 (14.5-22.0)	0.94

Statistical comparison and summary characteristics for primary eloquent glioblastoma patients from 2010-2020 for the unmatched and matched KPS cohorts.

Abbreviations: SD: standard deviation; IQR: interquartile range; KPS: Karnofsky Performance Score; ASA: American Society of Anesthesiology [score]; NIHSS: National Institute of Health Stroke Scale; IDH: iso-citrate dehydrogenase; MGMT: promotor region of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase; CE: contrast enhancing; CTx: chemotherapy; RTx: radiotherapy.

eTable 5: Factors independently impacting overall survival (Multivariate Cox proportional-hazards regression, matched cohorts)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Gender														
Male	1.23 (0.97-1.57)	0.092	0.74 (0.54-1.02)	0.062	1.63 (0.77-3.24)	0.20	0.95 (0.53-1.73)	0.87	2.36 (1.29-4.32)	0.005	1.17 (0.80-1.72)	0.42	1.01 (0.61-1.66)	0.98
Female	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Mean age at diagnosis	1.01 (1.00-1.03)	0.013	1.03 (1.01-1.04)	0.0041	0.93 (0.85-1.02)	0.13	1.03 (1.01-1.06)	0.012	1.02 (0.99-1.05)	0.27	1.01 (1.00-1.03)	0.091	1.01 (0.99-1.04)	0.40
Preoperative KPS														
90-100	0.62 (0.46-0.82)	<0.001	0.46 (0.32-0.67)	<0.001	1.06 (0.46-2.43)	0.90	0.87 (0.41-1.87)	0.72	0.62 (0.31-1.23)	0.17	NA		NA	
≤ 80	1.22 (0.88-1.70)	0.24	NA		0.88 (0.50-1.53)	0.64	1.17 (0.60-2.27)	0.65	3.13 (0.69-14.3)	0.14	NA		NA	
Preoperative ASA score														
I	1.02 (0.51-2.02)	0.96	2.04 (0.87-4.76)	0.10	0.10 (0.01-1.74)	0.11	0.98 (0.36-2.65)	0.97	0.15 (0.04-0.50)	0.002	1.30 (0.98-1.72)	0.071	0.02 (0.00-0.19)	0.001
II	1.10 (0.59-2.07)	0.76	1.38 (0.64-3.01)	0.41	106.3 (0.72-Inf)	0.067	0.67 (0.30-1.50)	0.33	0.75 (0.39-1.45)	0.39	0.89 (0.63-1.27)	0.53	0.01 (0.00-0.08)	0.001
III	1.33 (0.69-2.55)	0.40	1.98 (0.63-1.39)	0.095	3300.3 (1.28-Inf)	0.043	NA		1.97 (0.58-6.67)	0.28	1.83 (1.25-2.69)	0.002	0.01 (0.00-0.08)	0.001
IV	NA		NA		NA		NA		NA				NA	
Preoperative NIHSS score														
0-1	0.75 (0.10-5.95)	0.79	0.93 (0.63-1.39)	0.73	1.98 (0.63-6.25)	0.24	NA		NA		0.46 (0.28-0.76)	0.002	0.74 (0.43-1.25)	0.26
≥ 2	1.03 (0.13-8.21)	0.98	NA		1.39 (0.81-2.41)	0.24	NA		NA		1.87 (1.21-2.88)	0.005	1.13 (0.76-1.67)	0.56

eTable 5: Factors independently impacting overall survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Tumor location by lobe														
Frontal	0.70 (0.36-1.35)	0.29	0.35 (0.11-1.09)	0.070	1.41 (0.77-2.59)	0.27	2.00 (0.83-4.83)	0.12	0.75 (0.19-2.96)	0.68	0.52 (0.20-1.37)	0.18	1.34 (0.31-5.86)	0.70
Parietal	0.87 (0.47-1.63)	0.67	0.48 (0.17-1.41)	0.18	0.36 (0.12-1.06)	0.064	0.63 (0.23-1.74)	0.37	0.85 (0.23-3.16)	0.81	0.63 (0.26-1.57)	0.32	1.97 (0.48-8.11)	0.35
Temporal	0.78 (0.41-1.50)	0.46	0.48 (0.16-1.42)	0.18	0.26 (0.05-1.30)	0.10	0.23 (0.04-1.25)	0.088	1.11 (0.25-4.91)	0.89	0.66 (0.25-1.73)	0.40	1.46 (0.34-6.19)	0.61
Occipital	NA		NA		NA		1.14 (0.15-8.50)	0.90	1.47 (0.29-7.42)	0.64	1.03 (0.49-2.15)	0.93	0.57 (0.20-1.61)	0.29
Insula	NA		NA		NA		NA		NA		NA		NA	
Tumor location by hemisphere														
Left	0.62 (0.45-0.86)	0.0045	0.90 (0.57-1.42)	0.65	0.33 (0.11-1.02)	0.054	0.76 (0.34-1.73)	0.52	0.77 (0.30-1.95)	0.58	0.70 (0.44-1.11)	0.13	1.00 (0.44-2.26)	1.00
Right	NA		Ref		Ref		Ref		Ref		Ref		Ref	
Tumor location by eloquence														
Motor	0.82 (0.60-1.11)	0.20	1.03 (0.66-1.60)	0.91	0.39 (0.14-1.11)	0.077	2.28 (1.07-4.85)	0.032	0.66 (0.32-1.95)	0.25	0.81 (0.51-1.29)	0.37	0.47 (0.27-0.83)	0.009
Sensory	0.64 (0.38-1.06)	0.083	0.63 (0.32-1.24)	0.18	2.47 (0.31-19.6)	0.39	1.26 (0.46-3.50)	0.65	1.70 (0.48-6.04)	0.41	0.71 (0.34-1.50)	0.37	1.01 (0.25-4.00)	0.99
Language	1.35 (0.94-1.96)	0.11	1.59 (0.94-2.67)	0.081	2.30 (0.74-7.14)	0.15	2.99 (1.25-7.16)	0.014	0.78 (0.32-1.89)	0.58	1.37 (0.78-2.41)	0.28	0.96 (0.45-2.03)	0.92
Visual	1.10 (0.70-1.74)	0.68	1.10 (0.61-1.98)	0.76	0.17 (0.03-0.86	0.032	1.93 (0.50-7.45)	0.34	2.14 (0.81-5.65)	0.12	0.72 (0.35-1.45)	0.35	0.82 (0.32-2.10)	0.67

eTable 5: Factors independently impacting overall survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
IDH status														
Wildtype	3.92 (1.73-8.87)	0.0011	4.00 (1.74-9.19)	0.001	NA		3.28 (1.42-7.59)	0.006	NA		3.68 (1.48-9.15)	0.005	NA	
Mutant	Ref		Ref				Ref				Ref			
MGMT status														
Methylated	1.00 (0.74-1.35)	1.00	0.82 (0.55-1.23)	0.34	0.86 (0.45-1.63)	0.64	1.05 (0.68-1.61)	0.83	1.46 (0.54-3.96)	0.46	0.93 (0.60-1.43)	0.74	0.89 (0.53-1.50)	0.66
Unmethylated	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Surgical adjuncts														
Awake craniotomy	1.26 (0.92-1.74)	0.16	1.10 (0.76-1.59)	0.62	0.23 (0.06-0.88)	0.033	1.27 (0.67-2.40)	0.47	3.07 (1.25-7.53)	0.014	0.98 (0.66-1.46)	0.93	1.65 (0.86-3.15)	0.13
Intraoperative ultrasound	1.61 (1.12-2.30)	0.010	1.71 (1.09-2.69)	0.020	4.14 (1.34-12.8)	0.014	1.54 (0.67-3.56)	0.31	1.98 (0.81-4.83)	0.13	1.60 (0.90-2.86)	0.11	0.85 (0.43-1.68)	0.65
Intraoperative fluorescence	1.45 (1.06-1.98)	0.020	1.57 (1.10-2.26)	0.014	2.34 (0.72-7.65)	0.16	0.27 (0.07-0.99)	0.049	2.74 (1.34-5.60)	0.006	1.51 (0.98-2.31)	0.060	1.70 (0.84-3.44)	0.14
6-week NIHSS, pre-op ref														
Deteriorated	1.46 (1.12-1.91)	0.005	1.89 (1.30-2.75)	<0.001	1.28 (0.61-2.68)	0.51	0.78 (0.33-1.88)	0.59	2.53 (0.98-6.53)	0.056	1.53 (1.06-2.20)	0.022	4.72 (2.27-9.82)	0.001
6-week KPS, pre-op as ref	2.18 (1.66-2.87)	<0.001	2.75 (1.88-4.03)	<0.001	1.92 (0.83-4.47)	0.13	0.86 (0.42-1.76)	0.67	2.52 (1.10-5.80)	0.029	1.50 (1.00-2.26)	0.052	1.48 (0.75-2.92)	0.25
Deteriorated														

eTable 5: Factors independently impacting overall survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Postoperative vascular complications														
None	1.21 (0.88-1.66)	0.25	1.31 (0.38-4.50)	0.67	0.08 (0.01-0.48)	0.005	NA		0.15 (0.04-0.56)	0.005	0.95 (0.27-3.37)	0.934	0.03 (0.01-0.19)	0.001
Major ischemia	1.31 (0.57-3.00)	0.52	3.10 (0.72-13.3)	0.13	NA		NA		NA		0.81 (0.15-4.44)	0.81	0.37 (0.06-2.33)	0.29
Rebleed	1.05 (0.31-3.54)	0.94	2.60 (0.49-13.8)	0.26	NA		NA		NA		1.48 (0.47-4.70)	0.51	31.9 (8.45-120)	0.001
Preoperative CE tumor volume														
0-10 ml	0.61 (0.33-1.10)	0.10	0.22 (0.10-0.48)	<0.001	6.33 (1.33-30.2)	0.021	1.30 (0.12-14.7)	0.83	0.21 (0.03-1.44)	0.11	0.72 (0.26-2.02)	0.53	0.35 (0.08-1.54)	0.16
10-25 ml	0.72 (0.43-1.20)	0.21	0.41 (0.21-0.82)	0.012	1.51 (0.52-4.37)	0.45	2.58 (0.28-23.9)	0.41	0.32 (0.09-1.18)	0.086	0.80 (0.31-2.04)	0.64	1.11 (0.40-3.05)	0.84
25-50 ml	0.59 (0.37-0.94)	0.028	0.37 (0.20-0.70)	0.002	3.73 (1.26-11.1)	0.018	2.78 (0.31-25.1)	0.36	0.11 (0.03-0.43)	0.001	0.67 (0.27-1.65)	0.38	0.88 (0.34-2.27)	0.80
50-100 ml	0.54 (0.34-0.87)	0.011	0.36 (0.19-0.68)	0.002	NA		2.56 (0.30-21.7)	0.39	0.01 (0.04-0.47)	0.002	0.72 (0.29-1.79)	0.48	0.54 (0.20-1.44)	0.22
>100 ml	NA		NA		NA		NA		NA		1.26 (0.61-2.60)	0.53	1.19 (0.63-2.27)	0.59

eTable 5: Factors independently impacting overall survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Postoperative CE tumor volume														
0-0.2 ml	0.44 (0.23-0.85)	0.015	0.65 (0.29-1.45)	0.30	0.08 (1.33-30.2)	0.004	0.15 (0.02-1.17)	0.070	0.07 (0.01-0.40)	0.003	0.45 (0.17-1.29)	0.12	0.89 (0.21-3.78)	0.88
0.2-1.0 ml	1.00 (0.58-1.72)	0.99	1.32 (0.70-2.50)	0.39	0.78 (0.52-4.37)	0.78	0.30 (0.07-1.36)	0.12	0.17 (0.03-0.98)	0.05	0.82 (0.39-1.73)	0.60	1.98 (0.54-7.27)	0.30
1.0-2.0 ml	0.65 (0.40-1.05)	0.081	1.15 (0.63-2.12)	0.65	1.25 (0.33-4.76)	0.75	0.19 (0.05-0.72)	0.015	0.25 (0.09-0.71)	0.009	0.67 (0.31-1.47)	0.32	0.84 (0.32-2.25)	0.73
>2.0 ml	NA		NA		NA		NA		NA		1.26 (0.86-1.84)	0.24	1.37 (0.87-2.15)	0.23
Extent of resection CE tumor														
98-100 %	0.93 (0.48-1.80)	0.83	0.57 (0.25-1.28)	0.17	11.4 (1.36-94.6)	0.025	22.9 (0.14-245)	0.10	5.17 (0.89-29.9)	0.067	1.15 (0.40-3.33)	0.79	0.37 (0.09-1.49)	0.16
95-98 %	0.83 (0.49-1.42)	0.50	0.44 (0.22-0.88)	0.021	NA		15.4 (2.90-81.8)	0.001	1.69 (0.44-6.51)	0.44	0.82 (0.33-2.23)	0.66	0.85 (0.30-2.39)	0.76
90-95 %	0.87 (0.57-1.30)	0.49	0.80 (0.47-1.36)	0.41	2.12 (0.52-8.41)	0.29	3.67 (0.73-18.4)	0.12	2.05 (0.76-5.53)	0.16	1.13 (0.61-2.10)	0.69	0.67 (0.32-1.38)	0.28
80-90 %	0.68 (0.46-1.02)	0.061	0.64 (0.36-1.13)	0.12	0.37 (0.10-1.43)	0.15	4.14 (1.02-16.8)	0.047	2.94 (1.04-8.33)	0.043	0.74 (0.40-1.37)	0.34	0.90 (0.38-2.13)	0.81
<80 %	NA		NA		NA		NA		NA		1.38 (0.88-2.16)	0.17	1.34 (0.82-2.21)	0.25

eTable 6: Factors independently impacting progression-free survival (Multivariate Cox proportional-hazards regression, matched cohorts)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Gender														
Male	0.94 (0.75-1.17)	0.57	0.81 (0.61-1.09)	0.16	1.51 (0.78-2.90)	0.22	0.78 (0.54-1.12)	0.18	0.75 (0.44-1.30)	0.31	0.90 (0.65-1.26)	0.54	0.95 (0.61-1.48)	0.82
Female	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Mean age at diagnosis	1.01 (1.00-1.02)	0.047	1.01 (0.99-1.02)	0.22	1.08 (0.99-2.90)	0.009	1.02 (1.00-1.04)	0.012	1.02 (0.99-1.05)	0.13	1.02 (1.0-1.03)	0.25	1.01 (0.99-1.04)	0.17
Preoperative KPS														
90-100	0.94 (0.72-1.22)	0.63	0.71 (0.51-1.00)	0.050	1.24 (0.55-2.78)	0.61	0.42 (0.27-0.66)	<0.001	2.74 (1.41-5.34)	0.003	NA		NA	
≤ 80	1.30 (0.97-1.75)	0.082	NA	NA	0.69 (0.40-1.18)	0.18	1.57 (1.02-2.41)	0.041	0.78 (0.51-1.18)	0.24	NA		NA	
Preoperative ASA score														
I	1.96 (1.01-3.80)	0.047	1.66 (0.75-3.67)	0.21	0.14 (0.01-2.21)	0.16	1.39 (0.76-2.56)	0.30	0.47 (0.15-1.44)	0.18	1.02 (0.79-1.32)	0.90	6.8 (1.15-40.6)	0.034
II	1.58 (0.86-2.89)	0.14	1.15 (0.55-2.39)	0.70	25.07 (0.32-194)	0.15	0.97 (0.61-1.55)	0.90	0.75 (0.41-1.38)	0.36	1.02 (0.75-1.32)	0.89	2.56 (0.47-13.9)	0.28
III	1.71 (0.92-3.18)	0.091	1.25 (0.60-2.62)	0.55	323.4 (0.26-Inf)	0.11	1.20 (0.85-1.69)	0.30	1.05 (0.64-1.71)	0.85	1.34 (0.97-1.85)	0.077	3.57 (0.65-19.7)	0.14
IV	NA		NA		NA		NA						NA	
Preoperative NIHSS score														
0-1	1.02 (0.13-7.98)	0.98	1.05 (0.72-1.53)	0.81	0.56 (0.18-1.73)	0.31	NA		NA		0.53 (0.33-0.86)	0.011	0.68 (0.43-1.06)	0.086
≥ 2	1.27 (0.16-9.95)	0.82	NA		1.55 (0.93-2.59)	0.094	NA		NA		1.50 (1.00-2.25)	0.050	1.23 (0.86-1.77)	0.26

eTable 6: Factors independently impacting progression-free survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Tumor location by lobe														
Frontal	0.80 (0.44-1.48)	0.49	0.43 (0.16-1.21)	0.11	1.77 (0.93-3.35)	0.082	2.63 (1.62-4.82)	<0.001	1.45 (0.46-4.56)	0.52	0.37 (0.15-0.91)	0.030	1.74 (0.55-5.51)	0.35
Parietal	0.85 (0.48-1.50)	0.57	0.41 (0.15-1.11)	0.081	0.70 (0.25-1.94)	0.49	0.58 (0.34-1.01)	0.056	1.03 (0.36-2.96)	0.96	0.44 (0.19-0.99)	0.048	1.37 (0.47-3.98)	0.57
Temporal	0.73 (0.40-1.34)	0.32	0.42 (0.15-1.14)	0.087	0.32 (0.07-1.57)	0.16	0.20 (0.08-0.51)	<0.001	1.52 (0.43-5.39)	0.52	0.40 (0.17-0.94)	0.036	1.40 (0.45-4.38)	0.56
Occipital	NA		NA		NA		2.16 (0.88-5.33)	0.095	0.77 (0.39-1.55)	0.47	1.39 (0.70-2.75)	0.35	0.64 (0.29-1.43)	0.28
Insula	NA		NA		NA		NA		NA		NA		NA	
Tumor location by hemisphere														
Left	0.78 (0.58-1.04)	0.087	0.79 (0.53-1.18)	0.26	0.46 (0.18-1.20)	0.11	1.79 (1.10-2.90)	0.019	1.96 (0.85-4.54)	0.12	0.63 (0.42-0.95)	0.026	1.22 (0.60-2.49)	0.59
Right	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Tumor location by eloquence														
Motor	0.85 (0.64-1.13)	0.27	0.91 (0.60-1.39)	0.67	0.47 (0.17-1.31)	0.15	0.74 (0.43-1.28)	0.28	0.60 (0.32-1.12)	0.11	1.02 (0.66-1.58)	0.92	0.78 (0.46-1.34)	0.37
Sensory	0.91 (0.59-1.41)	0.67	0.82 (0.45-1.48)	0.51	2.44 (0.40-14.8)	0.33	0.78 (0.42-1.45)	0.43	5.00 (1.34-18.6)	0.016	0.93 (0.50-1.74)	0.82	0.96 (0.82-10.7)	0.10
Language	0.13 (0.87-1.73)	0.25	1.46 (0.91-2.36)	0.12	1.80 (0.62-5.25)	0.28	1.22 (0.66-2.26)	0.52	0.78 (1.28-1.82)	0.57	1.78 (1.08-2.94)	0.025	1.15 (0.60-2.21)	0.68
Visual	0.97 (0.62-1.50)	0.88	0.99 (0.56-1.73)	0.96	0.24 (0.06-1.02)	0.053	0.32 (0.13-0.81)	0.016	1.73 (0.75-3.98)	0.20	0.70 (1.08-2.94)	0.28	0.22 (0.51-2.88)	0.66

eTable 6: Factors independently impacting progression-free survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
IDH status														
Wildtype	2.00 (1.06-3.77)	0.033	1.81 (0.92-3.55)	0.085	NA		1.79 (0.91-3.53)	0.094	NA		1.74 (0.81-3.74)	0.15	3.73 (0.51-27.5)	0.20
Mutant	Ref		Ref				Ref				Ref		Ref	
MGMT status														
Methylated	0.93 (0.72-1.20)	0.58	0.91 (0.65-1.27)	0.58	0.79 (0.45-1.41)	0.43	1.05 (0.62-1.28)	0.53	0.91 (0.51-1.63)	0.76	0.92 (0.65-1.31)	0.65	0.93 (0.58-1.50)	0.78
Unmethylated	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Surgical adjuncts														
Awake craniotomy	1.12 (0.85-1.48)	0.43	1.04 (0.75-1.42)	0.83	0.35 (0.08-1.53)	0.16	1.03 (0.71-1.50)	0.88	1.09 (0.50-2.37)	0.82	0.88 (0.62-1.25)	0.47	1.32 (0.72-2.41)	0.36
Intraoperative ultrasound	1.54 (1.12-2.12)	0.008	1.85 (1.25-2.73)	0.002	2.64 (0.89-7.85)	0.082	2.19 (1.38-3.46)	<0.001	1.16 (0.54-2.48)	0.71	2.01 (1.23-3.28)	0.005	0.96 (0.54-1.71)	0.88
Intraoperative fluorescence	1.12 (0.83-1.50)	0.46	1.40 (0.99-1.98)	0.054	0.98 (0.34-2.84)	0.97	1.77 (1.13-2.78)	0.013	0.78 (0.40-1.49)	0.44	1.50 (1.02-2.21)	0.040	0.76 (0.38-1.42)	0.43
6-week NIHSS, pre-op ref														
Deteriorated	1.69 (1.32-2.16)	<0.001	1.70 (1.22-2.37)	0.002	1.35 (0.67-2.73)	0.40	2.07 (1.34-3.20)	0.001	4.89 (1.97-12.1)	<0.001	1.14 (0.82-1.58)	0.45	2.45 (1.28-4.67)	0.007
6-week KPS, pre-op as ref														
Deteriorated	1.44 (1.12-1.85)	0.005	1.89 (1.36-2.61)	<0.001	0.76 (0.30-1.89)	0.55	1.51 (1.05-2.18)	0.027	0.50 (0.23-1.10)	0.084	1.95 (1.34-2.82)	<0.001	0.87 (0.46-1.64)	0.67

eTable 6: Factors independently impacting progression-free survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Postoperative vascular complications														
None	1.13 (0.84-1.52)	0.42	0.54 (0.15-1.92)	0.34	0.36 (0.08-1.69)	0.20	1.05 (0.35-3.19)	0.93	0.30 (0.08-1.06)	0.061	0.83 (0.24-2.91)	0.77	0.08 (0.02-0.39)	0.002
Major ischemia	1.55 (0.69-3.45)	0.29	1.09 (0.25-4.64)	0.91	NA		1.23 (0.29-5.16)	0.78			0.98 (0.19-5.16)	0.98	3.12 (1.37-7.10)	0.007
Rebleed	1.56 (0.49-5.00)	0.45	0.46 (0.09-2.48)	0.37	NA		NA				1.16 (0.37-3.65)	0.80	6.90 (2.03-23.5)	0.002
Preoperative CE tumor volume														
0-10 ml	0.52 (0.30-0.91)	0.022	0.31 (0.15-0.64)	0.001	6.52 (1.29-33.0)	0.023	0.26 (0.11-0.61)	0.002	0.34 (0.06-1.93)	0.22	0.61 (0.24-1.55)	0.30	0.21 (0.06-0.78)	0.019
10-25 ml	0.79 (0.50-1.25)	0.31	0.73 (0.39-1.34)	0.31	2.60 (0.86-33.0)	0.090	0.66 (0.34-1.29)	0.22	0.52 (0.16-1.69)	0.28	1.12 (0.49-2.55)	0.79	0.69 (0.30-1.62)	0.40
25-50 ml	0.54 (0.35-0.82)	0.004	0.51 (0.29-0.89)	0.018	3.54 (0.14-1.63)	0.018	0.52 (0.26-1.03)	0.059	0.13 (0.04-0.43)	<0.001	0.83 (0.38-1.85)	0.66	0.43 (0.19-0.97)	0.042
50-100 ml	0.53 (0.35-0.81)	0.004	0.71 (0.41-1.26)	0.24	NA		0.68 (0.34-1.36)	0.28	0.19 (0.06-0.57)	0.003	0.83 (0.37-1.87)	0.66	0.47 (0.21-1.08)	0.074
>100 ml	NA		NA		NA		NA		NA		1.01 (0.51-2.00)	0.97	1.59 (0.89-2.86)	0.12

eTable 6: Factors independently impacting progression-free survival (Multivariate Cox proportional-hazards regression, matched cohorts) (continued)

Group	**Overall [n= 512]**	*p*	**<70 [n=327]**	*p*	**≥ 70 [n=95]**	*p*	**NIHSS 0-1 [n=412]**	*p*	**NIHSS ≥ 2 [n=125]**	*p*	**KPS 90-100 [n=285]**	*p*	**KPS ≤ 80 [n=165]**	*p*
Characteristic	**HR**		**HR**		**HR**		**HR**		**HR**		**HR**		**HR**	
Postoperative CE tumor volume														
0-0.2 ml	0.56 (0.31-1.01)	0.054	0.78 (0.38-1.57)	0.48	0.20 (0.04-1.11)	0.065	0.41 (0.15-1.17)	0.095	0.61 (0.14-2.68)	0.52	0.42 (0.17-1.04)	0.060	2.27 (0.68-7.65)	0.18
0.2-1.0 ml	1.18 (0.71-1.96)	0.53	0.93 (0.51-1.70)	0.81	0.89 (0.16-4.91)	0.90	0.72 (0.32-1.63)	0.433	1.22 (0.31-4.85)	0.77	0.73 (0.36-1.46)	0.37	2.95 (0.97-9.01)	0.057
1.0-2.0 ml	0.76 (0.49-1.19)	0.23	0.94 (0.53-1.65)	0.82	0.49 (0.14-1.63)	0.24	0.61 (0.29-1.29)	0.20	0.38 (0.14-1.01)	0.052	0.67 (0.35-1.30)	0.24	1.05 (0.45-2.45)	0.92
>2.0 ml	NA		NA		NA		NA		NA		1.22 (0.88-1.69)	0.24	1.42 (0.93-2.16)	0.11
Extent of resection CE tumor														
98-100 %	0.95 (0.52-1.73)	0.87	0.68 (0.32-1.44)	0.31	3.28 (0.38-28.1)	0.28	1.07 (0.37-3.13)	0.90	1.03 (0.22-4.76)	0.97	1.38 (0.54-3.54)	0.50	0.19 (0.06-0.65)	0.008
95-98 %	0.80 (0.47-1.35)	0.40	0.68 (0.36-1.30)	0.24	NA		0.78 (0.35-1.76)	0.56	1.92 (0.50-4.85)	0.34	1.07 (0.48-2.39)	0.88	0.47 (0.18-1.25)	0.13
90-95 %	0.87 (0.60-1.27)	0.47	0.98 (0.59-1.65)	0.95	2.42 (0.73-8.08)	0.15	1.20 (0.62-2.32)	0.60	0.57 (0.23-1.44)	0.24	1.13 (0.64-1.98)	0.68	0.41 (0.21-0.80)	0.010
80-90 %	0.72 (0.49-1.04)	0.081	0.70 (0.40-1.22)	0.21	0.77 (0.26-2.28)	0.64	0.49 (0.26-0.91)	0.025	3.01 (1.21-7.47)	0.018	0.64 (0.37-1.10)	0.11	0.79 (0.38-1.62)	0.52
<80 %	NA		NA		NA				NA		1.19 (0.79-1.79)	0.41	1.52 (0.94-2.47)	0.088

CHAPTER 12

Global comparison of awake and asleep mapping procedures in glioma surgery: An international multicenter survey

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ABSTRACT

Background

Mapping techniques are frequently used to preserve neurological function during glioma surgery. There is however no consensus regarding the use of many variables of these techniques. Currently, there is almost no objective data available about potential heterogeneity between surgeons and centers. The goal of this survey is therefore to globally identify, evaluate and analyze the local mapping procedures in glioma surgery.

Methods

The survey was distributed to members of the neurosurgical societies of the Netherlands (NVVN), Europe (EANS) and the United States (CNS) between December 2020 and January 2021 with questions about awake mapping, asleep mapping, assessment of neurological morbidity, and decision making.

Results

Survey responses were obtained from 212 neurosurgeons from 42 countries. Overall, significant differences were observed for equipment and its settings that are used for both awake and asleep mapping, intraoperative assessment of eloquent areas, the use of surgical adjuncts and monitoring, anesthesia management, assessment of neurological morbidity, and perioperative decision making. Academic practices performed awake and asleep mapping procedures more often and employed a clinical neurophysiologist with telemetric monitoring more frequently. European neurosurgeons differed from US neurosurgeons regarding the modality for cortical/subcortical mapping and awake/asleep mapping, the use of surgical adjuncts and anesthesia management during awake mapping.

Discussion

This survey demonstrates the heterogeneity among surgeons and centers with respect to their procedures for awake mapping, asleep mapping, assessing neurological morbidity and decision making in glioma patients. These data invite further evaluations as for key variables that can be optimized and may therefore benefit from consensus.

INTRODUCTION

Gliomas are the most common form of primary brain malignancy in adults and the current standard treatment consists of maximum safe surgery [1,2]. For gliomas that are located in or near eloquent areas, the oncological goal of resection - tumor cytoreduction – is often at conflict with the functional goal – preventing neurological deficits [3-11]. The surgeon can choose from a wide array of surgical and nonsurgical modalities to help him balance between both goals. For this purpose, mapping techniques are one of the most frequently used modalities. There is however no consensus regarding the choice of surgical modality and there are no existing guidelines regarding the indications for mapping techniques, tools for choosing between different mapping modalities, specific settings for intraoperative mapping techniques, and so forth. This lack of consensus may have resulted in a large heterogeneity between surgeons and centers with respect to these variables. The extent of this heterogeneity has never been assessed objectively, although certain aspects of the procedure may very well benefit from consensus, which may be advantageous for future collaborative efforts as well.

The goal of this survey is therefore to globally identify, evaluate and analyze the local procedures of mapping techniques in glioma surgery. The results will subsequently serve as a first stepping-stone towards potential consensus on certain aspects and as a starting point for future collaboration.

MATERIALS AND METHODS

Survey design

The questionnaire was constructed by a panel of neurosurgeons from Europe and the United States with ample experience with mapping techniques for glioma resections as part of the ENCRAM Research Consortium. It has been conducted in compliance with the principles of the Declaration of Helsinki (2013) and the General Data Protection Regulation (GDPR) (2018). Question subgroups included awake mapping, asleep mapping, the assessment of neurological morbidity and intraoperative decision making. Questions were aimed to evaluate the local mapping procedures, especially regarding equipment and its settings, intraoperative assessment of eloquent areas, use of surgical adjuncts, anesthesia techniques for mapping procedures, assessment and registration of neurological morbidity, management of mapping-induced seizures and intraoperative decision making. The target audience included consultant neurosurgeons (attendings) and neurosurgery fellows. These providers were divided in 3 groups: neurosurgery consultants/attendings with >5 years as experience as a neurosurgeon after their residency, neurosurgery consultants/attendings

with <5 years as experience, and neurosurgery fellows. Additional baseline characteristics included country, gender, number of glioma resections performed and affiliation.

Survey distribution

The survey was made available by a link to the online LimeSurvey questionnaire platform (LimeSurvey GmbH, Hamburg, Germany) and was distributed twice by electronic mailing lists of the Congress of Neurological Surgeons (CNS) and the Dutch Neurosurgical Association (NVVN) with Mailchimp (Atlanta, GA, USA). It was included twice in the monthly newsletter of the European Association of Neurological Societies (EANS). Participation in the survey was anonymous, voluntary and without remuneration. Response rate was 3.7% among CNS members and 17.8% among NVVN members. Response rate among EANS members could not be assessed due to the nature of the survey's dispersal. The survey was open for entries between December 2020 and January 2021.

Statistical analysis

Survey data were exported for further data analysis on January 19th, 2021 from LimeSurvey into an Excel file and analyzed using *R* version 4.0.3 (the *R* foundation, Vienna, Austria). Data were grouped according to the baseline characteristics gender, WHO region, affiliation, surgeon training level and the number of glioma resections the surgeon had performed. Overall response differences were analyzed using the χ^2 test for proportions with the Marascuillo procedure and Bonferroni correction for multiple testing. For responses with an observed count of <10 and/or expected count of <5 the Fisher's exact test was used. Differences in survey responses based on the surgeon's experience (in terms of number of glioma resections performed) were analyzed using the same statistical tests as for the overall response differences. Categorical survey responses were further analyzed for different subgroups using multivariate logistic (logit) regression with type of institute and region (Europe/US) as the two independent variables. For variables with >2 response options, dummy coding was used for processing responses into dichotomous variables. For questions that allowed multiple answers, the McFadden MNL model was used as a mixed effects model to analyze subgroup responses. Continuous survey outcomes were analyzed using multinominal linear regression. Statistical significance was set at 5%.

RESULTS

We obtained a total of 212 responses from 42 countries. Table 1 (Data Supplement) shows the baseline characteristics of the respondents. 192 survey participants were male (90.1%) and 20 participants were female (9.9%). Forty percent of the responses originated from the United States and Canada (*n*=85), 11.8% from Latin America (*n*=25), 32.5% from Europe

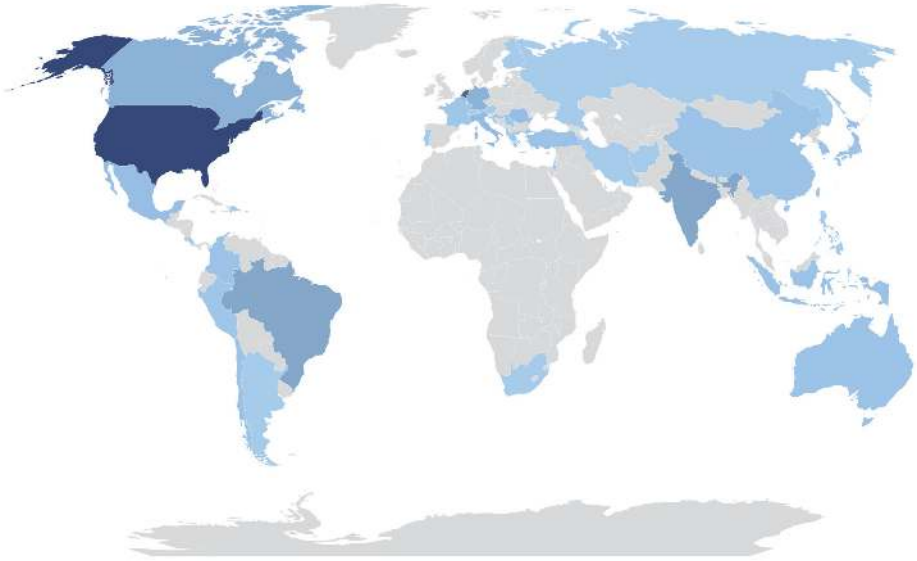

Figure 1: Survey respondents by country

(*n*=69), 0.94% from the Eastern Mediterranean Region (*n*=2), 6.6% from South-East Asia (*n*=14), 7.5% from the Western Pacific (*n*=16) and 0.5% from the African Region (*n*=1) (Table 1, Figure 1, Data Supplement). 58.8% of participants was appointed at an academic practice/university hospital (*n*=124), 18.9% worked at a non-academic practice/community hospital (*n*=40), 18.4% was appointed at a private practice (*n*=39) and 4.2% selected "other" as their current appointment (*n*=9) (Table 1). The majority of survey respondents concerned consultant neurosurgeons with >5 years of practice after finishing their fellowship (79.9%, *n*=169), 14.2% still had less than 5 years of experience (*n*=30). 3.3% of respondents were currently appointed as neurosurgical fellow (*n*=7), and 2.8% selected "other" as their current training level (*n*=6) (Table 1). Experience with glioma surgery differed between respondents: 28.8% had performed less than 100 glioma resections (*n*=61), 47.2% had performed between 100 and 500 resections (*n*=100) and 24.1% had performed more than 500 resections (*n*=51) (Table 1).

Overall responses

Awake craniotomy – settings

Overall responses were significantly different for 21 of the 31 questions (Table 2 Data Supplement, Figure 2). Ninety-seven of the 212 neurosurgeons reported the use of awake craniotomies at their institution. Among them, the majority used direct electrostimulation with a handheld probe for cortical mapping (56.7%), whereas 34.9% preferred a subdural

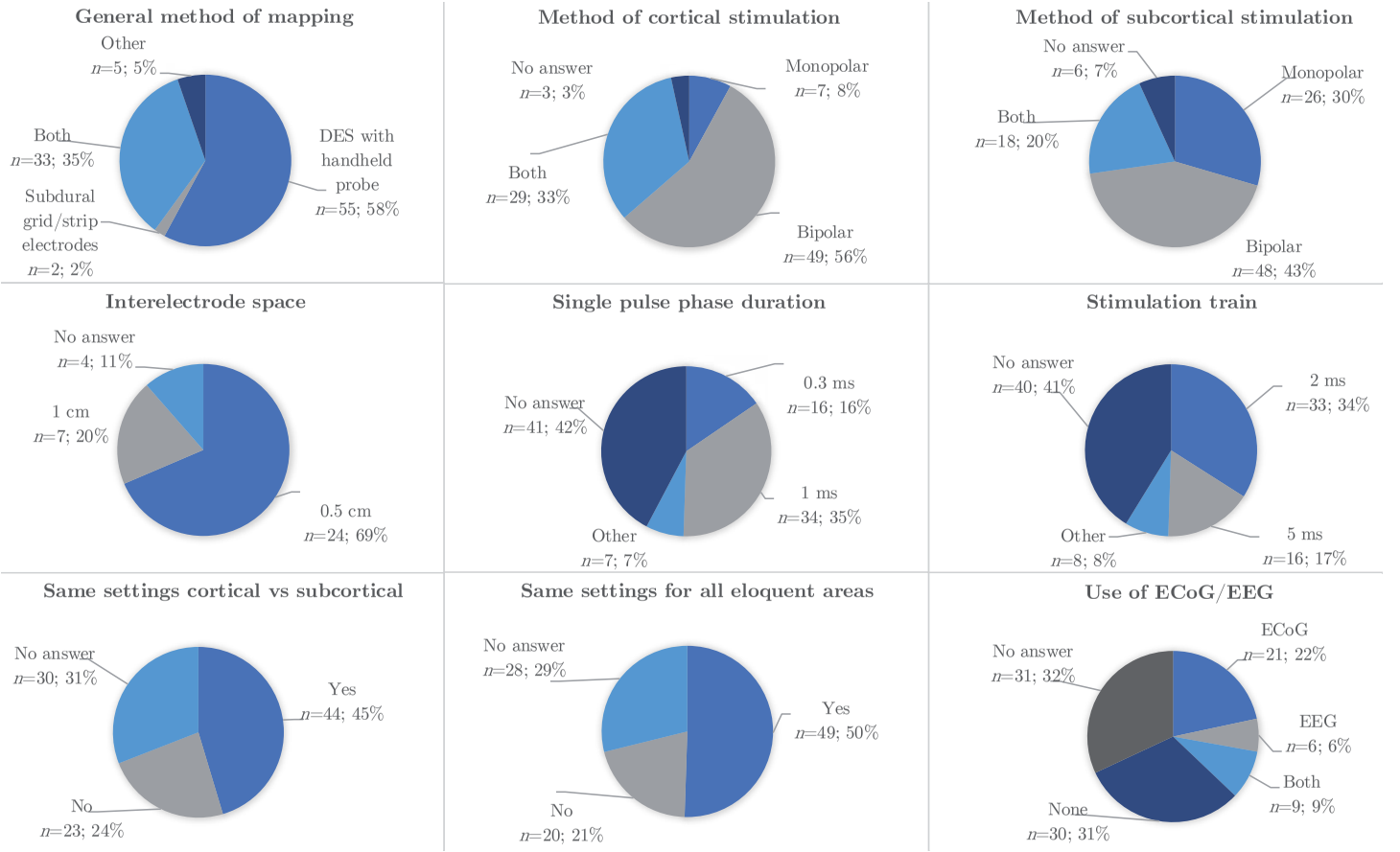

Figure 2: Significant differences – Awake mapping procedures

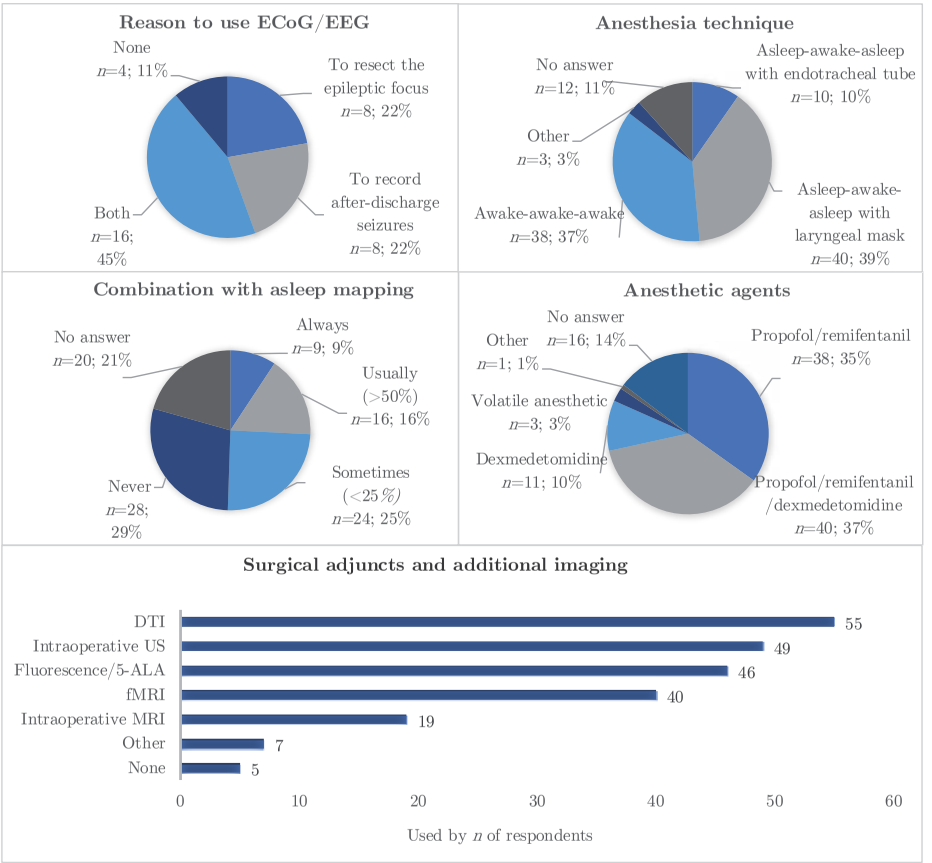

Figure 2: Significant differences – Awake mapping procedures (continued)

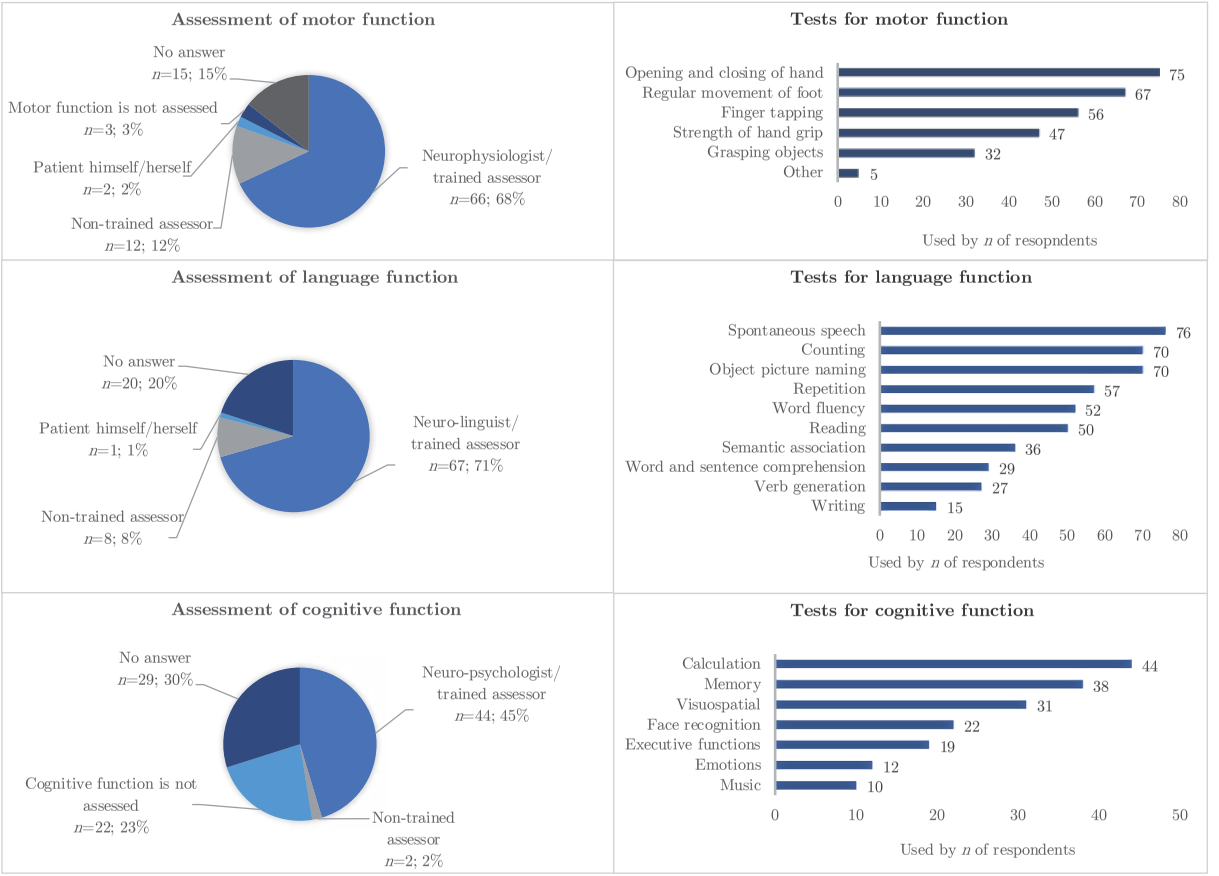

Figure 2: Significant differences – Awake mapping procedures (continued)

grid or strip electrodes (p<0.0001). Most respondents who used a bipolar stimulator for cortical stimulation (55.7%) or both a monopolar and bipolar (36.4%, p=0.0104 for difference). For subcortical stimulation, 47.7% used only a bipolar stimulator, 29.5% used only a monopolar stimulator (p=0.0134) and 20.5% used both (p=0.0001). Among neurosurgeons who used subdural grid or strip electrodes, most of them used an interelectrode space of 0.5 cm (68.6%) (p<0.0001). The median limits for current range during awake cortical mapping were 2 mA-10 mA. Current's increasing steps and stimulation frequencies did not differ significantly. The single pulse phase duration (SPPD) was more often 1.0 ms (35.1%) than 0.3 ms (15.5%,) (p=0.0017) and the majority of respondents reported a train of 2 sec (34.0%) as opposed to 5 sec (16.5%) (p=0.0051). Most respondents used the same stimulation settings for all awake cortical mapping procedures (50.5%) and for cortical and subcortical mapping (45.4%) (p=0.0015).

Awake craniotomy – assessment of eloquent areas

The majority of respondents reported that eloquent areas were assessed by a trained assessor (68.0% for motor, 69.1% for speech and 45.4% for cognition) (Table 2 Data Supplement, Figure 2). Motor function was most commonly assessed by opening and closing of the hand (79.8%), regular movement of the foot (71.3%); language function by spontaneous speech production (78.4%), counting (72.2%) and object picture naming (72.2%); and cognitive function with calculation (100%), memory (86.4%) and visuospatial functioning (70.5%).

Awake craniotomy – monitoring, surgical adjuncts and anesthesia management

Slightly more than half of the surgeons who performed awake craniotomies combines this sometimes (24.7%) or never (28.9%) with asleep mapping during the same resection (Table 2 Data Supplement, Figure 2). DTI (56.7%) and intraoperative ultrasound (50.5%) are the most frequently used surgical adjuncts, followed by fluorescence/5-ALA (47.4), functional MRI (fMRI) (41.2%) and intraoperative MRI (19.6%) (p<0.0001). Most neurosurgeons either use only ECoG (21.6%) or no electrophysiological monitoring at all (30.9%) (p=0.0005). When ECoG and/or intraoperative EEG are used, they are most frequently used to record both after-discharge seizures and to resect the epileptic focus (44.4%) (p=0.0011). For anesthesia management, the adjusted asleep-awake-asleep technique with laryngeal mask (41.2%) and awake-awake-awake technique (39.2%) were used most often (p<0.0001). Either a combination propofol/remifentanil (39.2%) or propofol/remifentanil/dexmedetomidine (41.2%) were used the most frequently for anesthesia induction (p<0.0001).

Asleep mapping

Overall responses were significantly different for 8 of the 18 questions (Table 3 Data Supplement, Figure 3). Seventy-seven (36.3%) respondents reported the use of asleep mapping techniques at their institute. For cortical mapping, a slight majority preferred the

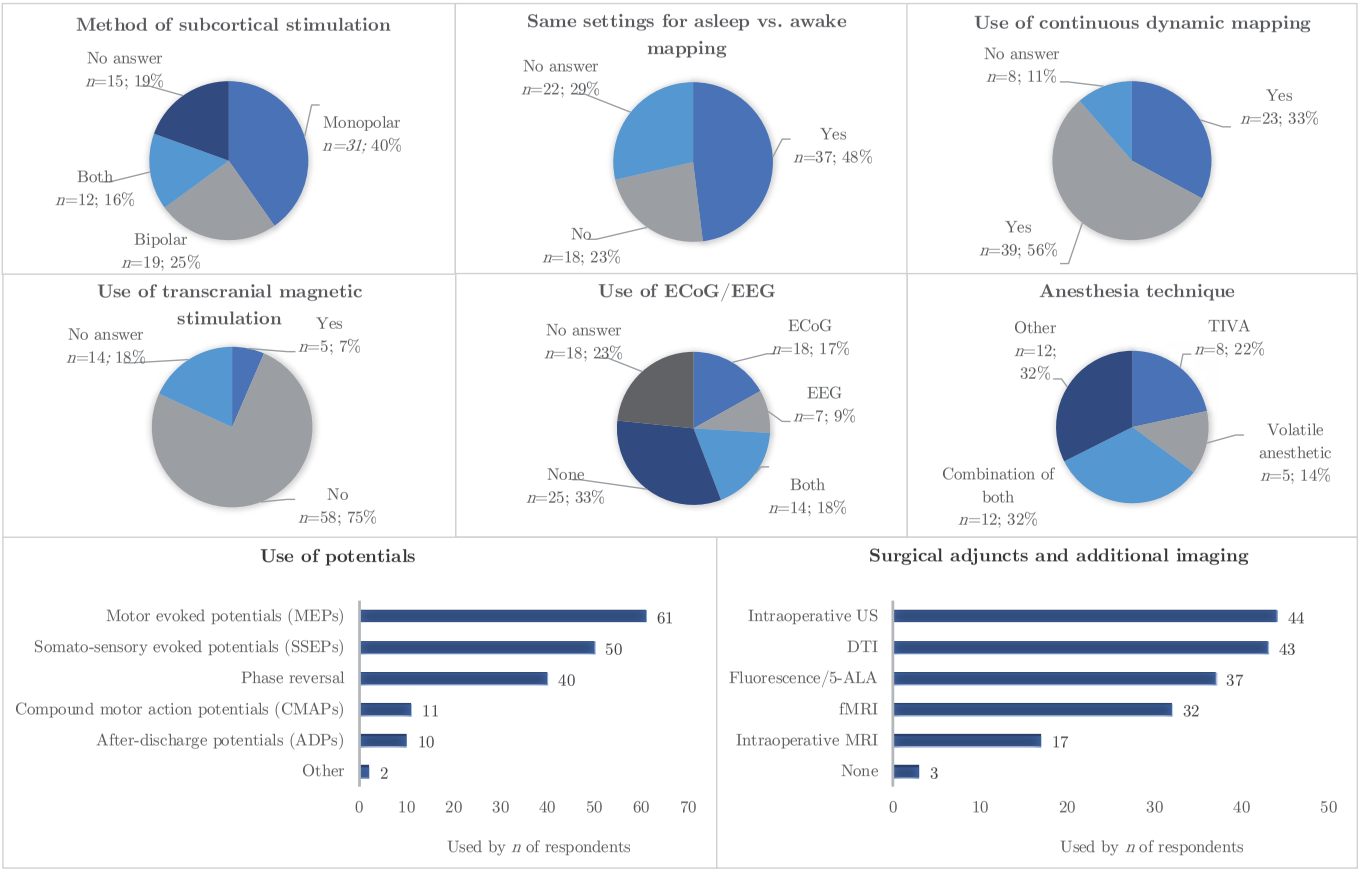

Figure 3: Significant differences – Asleep mapping procedures

combination of a monopolar and bipolar stimulator (36.4%) or a bipolar stimulator alone (29.9%). For subcortical mapping, most neurosurgeons used the monopolar only (40.3%) (p=0.0007). For the majority of them, the stimulation settings for asleep mapping were the same as for awake mapping (48.1% versus 23.4%, p=0.0014).

The minority of neurosurgeons used continuous dynamic mapping (CDM) for asleep mapping techniques (29.9%) (p=0.0090). Furthermore, only 6.5% of respondents reported that they used transcortical magnetic stimulation (TMS) for asleep mapping (p<0.0001). Eloquent areas were most commonly identified using evoked potentials (MEPs: 79.2%, SSEPs: 64.9%) or phase reversal (51.9%) (p<0.0001). The majority of neurosurgeons reported the presence of a clinical neurophysiologist during asleep mapping procedures, either with telemetric monitoring (39.0%), or without (28.6%). The most common surgical adjuncts of modalities for additional imaging were fMRI (41.6%), fluorescence/5-ALA (48.1%), diffusion tensor imaging (DTI, 55.8%) and intraoperative ultrasound (57.1%) (p<0.0001). A majority of neurosurgeons did not use ECoG or EEG intraoperatively during asleep mapping procedures (32.5%) (p=0.0004), and general anesthesia was most frequently induced by total intravenous anesthesia (TIVA, 62.3%) (p<0.0001).

Assessment of neurological morbidity

Most of the respondents reported that neurological morbidity is documented as free text in the electronic patient system at their institute (77.5%) (p<0.0001) (Table 4 Data Supplement, Figure 4). In contrast, a majority of survey participants reported that they would prefer to assess neurological morbidity using a standardized scale (61.6%) (p<0.0001). Neurosurgeons were the most common assessors of neurological morbidity in our survey (92.0%), followed by neurosurgical residents (40.6%), neurologists (29.7%), and physician assistants (25.4%).

Decision making

The most common reason among respondents to perform an awake craniotomy in glioma patients was the possibility to perform mapping or monitoring in an *awake* setting (56.2%, p<0.0001) (Table 5 Data Supplement). Documentation of the stimulation threshold and intensity in relation with eloquent mapping sites (39.7%) was most common, followed by information regarding the neuronavigation (29.8%), and information regarding the evoked potentials (28.1%) (Table 3). On a scale of 1-10, the most important information on which neurosurgeons based their decision to end the resection is the patient's task performance (median 10) followed by the evoked potentials (median 9), the imaging (median 8) and the macroscopical view (median 8).

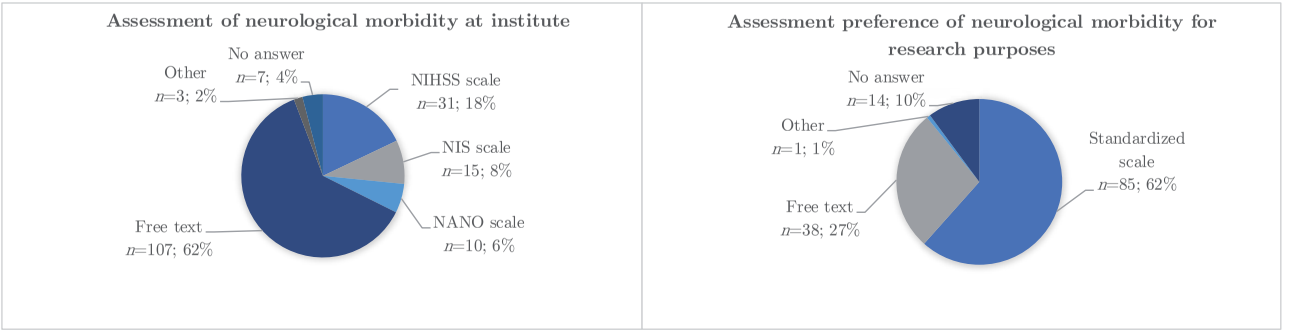

Figure 4: Significant differences – Assessment of neurological morbidity

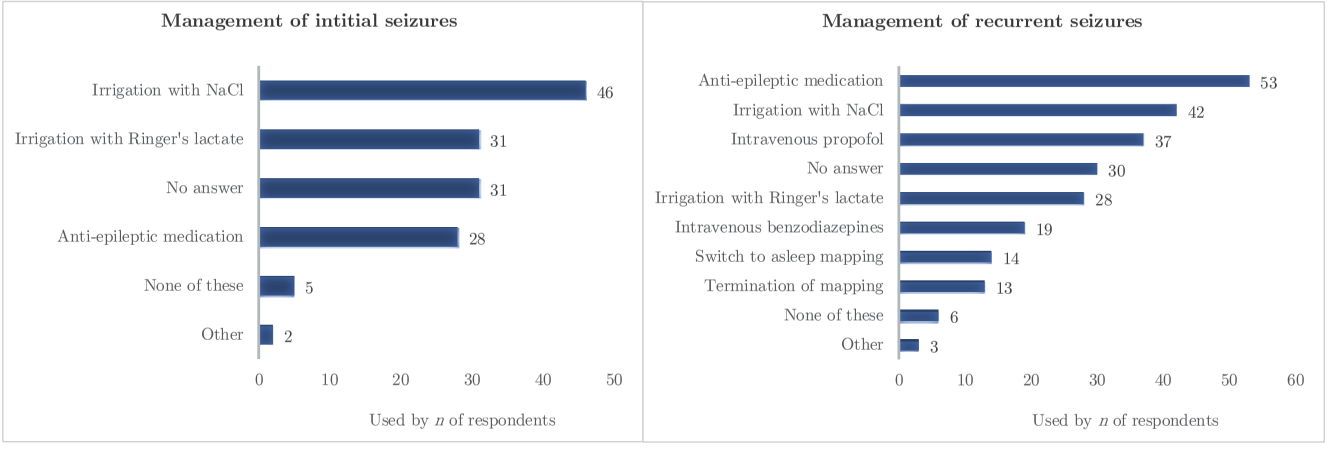

Figure 5: Significant differences – Decision making

Initial stimulation-induced seizures were most commonly suppressed by irrigation of the exposed brain surface with chilled sodiumchloride (NaCl) or Ringer's lactate solution (38.0% and 25.6%), or administration of anti-epileptic medication (23.1%) (p=0.0120) (Figure 5).

Recurrent stimulation-induced seizures were more commonly treated with anti-epileptic medications (43.8%) than irrigation of chilled NaCl (34.7%) or Ringer's lactate solution (23.1%) (p=0.0271) (Figure 5).

Subgroup responses

Responses were further analyzed according to the respondent's affiliation and region: academic practice/university hospital versus non-academic practice/community hospital or private practice; and Europe versus the United States.

Responses by center (academic versus non-academic or private practice)

For 5 of the 57 questions, significant differences were found between subgroups (Tables 2-5, Data Supplement). Academic neurosurgeons were more than five times as likely to perform awake craniotomies (OR=5.15, p=0.0007). Academic neurosurgeons also reported the use of asleep mapping techniques more than three times as often (OR= 3.56, p=0.0094). In academic centers, it was more common to have a clinical neurophysiologist present with telemetric monitoring during asleep mapping procedures: OR=6.00 (p=0.0278).

Responses by region (Europe versus United States)

For 9 of the 57 questions, significant differences were found between subgroups (Tables 2-5, Data Supplement). European neurosurgeons were less likely to report using a subdural grid/strip electrode alone (OR=0.28, p=0.0144) or in combination with a handheld probe for direct electrostimulation (OR=0.31, p=0.0245) during awake craniotomy. They assessed cognitive function more often during awake craniotomy (OR=4.03, p=0.0313) and used fluorescence/5-ALA intraoperatively (OR=3.77, p=0.0124) more frequently. They were less likely to use intraoperative MRI though (OR=0.23, p=0.0343). With respect to anesthesia management, European colleagues more often used propofol/remifentanil (OR=3.97, p=0.0124), whereas in the US they preferred the addition of dexmedetomidine to this regimen more commonly (OR=0.15, 95% CI=0.050-0.48, p=0.0012). During asleep mapping, European neurosurgeons were more likely to use continuous dynamic mapping (OR=6.26, p=0.0314), but less likely to use compound motor action potentials (CMAPs; OR=0.17, p=0.0493) or phase reversal (OR=0.21, p=0.0103) for the identification of eloquent areas. They also more often reported to have the clinical neurophysiologist present without telemetric monitoring during asleep mapping procedures (OR=5.91, p=0.0485).

Responses by surgeon's experience

For 2 of the 40 questions, significant differences were found between subgroups (Tables 6-8, Data Supplement). During awake mapping, the most experienced neurosurgeons (>500 glioma resections performed) used less often DES with a handheld probe (37.1%) than less experienced neurosurgeons (100-500 glioma resections performed: 65%; <100 glioma resections performed: 72.7%). Conversely, they used a combination of a handheld probe and a subdural grid or strip electrodes (54.3% versus 30.0% for the 100-500 subgroup and 9.1% for the <100 subgroup) (p=0.0009). Second, when more experienced neurosurgeons used a subdural grid or strip electrodes, more often the interelectrode space of the grid or strip was 1 cm (65.0%) than was the case during resections done by less experienced neurosurgeons (100-500 subgroup: 16.7%; <100 subgroup: 33.3%) (p=0.0085).

DISCUSSION

Key results

This survey is the first to investigate the local procedures regarding mapping procedures in glioma resections on a global scale, and further sub analyzed by institute and region.

We found an evident heterogeneity among surgeons and centers with respect to their local procedures. Overall, the most notable differences were observed for the kinds of equipment and its settings that are used for both awake and asleep mapping, the intraoperative assessment of eloquent areas, the use of surgical adjuncts, the use of monitoring, the anesthesia management, the assessment of neurological morbidity and the perioperative decision making. Academic practices more often performed awake and asleep mapping procedures and more often employ a clinical neurophysiologist with telemetric monitoring more often. There were significant differences in preference among European versus US neurosurgeons regarding the modality for cortical and subcortical mapping, the use of surgical adjuncts and anesthesia management for awake mapping. Furthermore, for asleep mapping, there were differences regarding the use of continuous dynamic mapping, the kind of evoked potentials that is being used, and the addition of telemetric monitoring. Last, more experienced neurosurgeons (in terms of glioma resections performed) used more often a combination of a probe and subdural grid/strip for awake mapping whereas less experienced neurosurgeons more frequently used a probe only.

Interpretation and comparison with the literature

The results from this survey should be interpreted in the perspective of previous conducted surveys. In 2017, Spena *et al* found in a survey among 20 European centers a substantial amount of heterogeneity between centers: some only performed awake mapping, and some

only asleep mapping [13]. In our survey, 40.4% performed both awake and asleep mapping, 23.8% only awake mapping and 9.9% only asleep mapping. Furthermore, Spena *et al* found that 53% used ECoG or EEG, which corresponded well with our results (37.1% during awake mapping, 44.2% during asleep mapping). Hamberger *et al* [14] found in a survey among 56 epilepsy centers evident variability in all aspects of the procedure. We found similar variability in our survey and share their conclusion that "this will influence mapping results, which directly affect the boundaries of cortical resection and, consequently, might worsen either seizure or functional outcomes". We would like to add that increased consensus on certain aspects would be beneficial in terms of collaborative scientific efforts between centers. A recent survey conducted by Arzoine *et al* [15] explored among 20 European centers the local practices in anesthetic management during low-grade glioma surgery. Their results were relatively similar to ours (ours in parenthesis): for awake surgery, 56% used the asleep-awake-asleep technique (51.5%), and 40% the awake-awake-awake technique (39.2%). For asleep surgery, 82% used a laryngeal mask (80%).

Few studies exist that have compared the outcomes of different mapping settings. Szelényi *et al* reported that stimulation-induced seizures are more frequent with the 50/60 Hz bipolar stimulation than with the train-of-five technique using strip electrodes or a monopolar stimulator [16]. They promote the use of this technique for both cortical and subcortical mapping and state that monopolar stimulation is more effective for subcortical mapping of the corticospinal tract than bipolar stimulation [17]. In contrast, Yamaguchi *et al* reported that the use of a bipolar stimulator for subcortical stimulation can be performed safely, which has been described by Berger *et al* as early as in 1990 and has since then become the gold standard for cortical mapping [18,19]. In our survey, we observed the contrasts between these studies as well: we found that 90.1% used a monopolar or bipolar for mapping during awake craniotomies. Among them, the majority used a bipolar for cortical (55.7%) and subcortical (47.7%) stimulation. For asleep mapping, comparable proportions of respondents used a monopolar (23.4%), bipolar (29.9%) or both (36.4%) for cortical mapping. For subcortical mapping, the majority used a monopolar (40.3%), rather than a bipolar (24.7%) or both (15.6%).

Our results are in line with the 2012 recommendations from the Japan Awake Surgery Conference [20,21], in which they state that cortical stimulation should be performed with a bipolar stimulator (current range 2-8 mA with 1 mA increments, SPPD 0.5 ms, frequency 50 Hz, duration 1-2 seconds) with seizure monitoring using ECoG. In our survey, the majority used a bipolar stimulator with a median current range of 2-12 with 1 or 2 mA increments, SPPD 1 ms, frequency 50 Hz (Europe) or 60 Hz (US) with a train of 2 seconds.

Limitations and strengths

An important limitation of survey studies is self-selection sampling bias. We assume that this survey was subject to this kind of bias as well, since a number of surgeons and centers have not responded to the survey. Moreover, low-to middle income counties may have to interpret the results of this study with caution since the responses were skewed towards Western high-income countries. The subgroup analyses that were conducted for institute and region focused on those countries as well which may have limited the external generalizability. Furthermore, a majority of respondents reported that the assessment of eloquent areas during mapping procedures were performed by highly trained personnel (neurophysiologists, neuro-linguists or trained assessors). We acknowledge that this would have implications on the generalizability of best practices to centers or countries with a lower density of resources. Due to the survey design, we were not able to investigate the interplay between the surgeon's personal preference and the institute's tradition on the choice for certain variables. We were also not able to directly compare the impact of procedural heterogeneity on surgical outcomes: therefore we chose to correlate survey responses with surgeon's experience as a proxy for impact on outcomes as the experience has likely evolved over time towards Level 4 practice patterns. Last, we noticed a relatively high proportion of "no answers" to certain questions (in particular regarding the technical details of the mapping procedure) which may be explained by the inability of responders to invest a larger amount of time in completing the survey. A closer look at our data revealed that the percentage of "no answers" was lower when the respondent had more experience in terms of number of glioma resections performed. Consequently, we cannot state unequivocally that time constraints were the only factor at play and we cannot fully exclude a relative lack of technical understanding as a possible cause of this issue. Therefore, we imagine that the results of this survey could potentially serve as an instrument to gain insight into novel opportunities for education. Important strengths of this study include the scale of distribution, the width of the survey's scope, the detail of the questions, the subgroup analyses between EU and US neurosurgeons and academic versus non-academic centers and the subgroup analyses between more and less experienced neurosurgeons.

Conclusions and future directions

This survey illustrates the evident heterogeneity between surgeons and centers regarding the specifics of mapping procedures and decision making. These results underline the importance for further research that addresses key aspects of mapping procedures and perioperative decision making. These aspects should be compared to identify the optimum framework for performing mapping procedures, taking into account local differences. The presented survey may serve as a first step towards a collaborative effort to investigate key variables that can be optimized and may therefore benefit from consensus. This will provide the neurosurgical field with the needed data on which clinical guidelines can be based in

order to reach the full potential of mapping in glioma resections. Further studies should focus on (1) the impact of procedural variability on surgical outcomes, ideally accompanied with a comparison between high-income and low-income countries and (2) the correlation of this observed variability among neurosurgeons with neuro-physiologists and anesthesiologists.

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DATA SUPPLEMENT

Table 1: Baseline characteristics

Characteristic	Number of responses (%) (*n* = 212)
Gender	
Male	192 (90.1)
Female	20 (9.9)
Region (World Health Organization)	
American Region – United States/Canada	85 (40.1)
American Region – Latin America	25 (11.8)
European Region	69 (32.5)
Eastern Mediterranean Region	2 (0.94)
South-East Asia Region	14 (6.6)
Western Pacific Region	16 (7.5)
African Region	1 (0.5)
Institute	
Academic practice/University hospital	124 (58.5)
Non-academic practice/Community hospital	40 (18.9)
Private practice	39 (18.4)
Other	9 (4.2)
Training level	
Consultant neurosurgeon, >5 years of experience	169 (79.7)
Consultant neurosurgeon <5 years of experience	30 (14.2)
Neurosurgical fellow	7 (3.3)
Other	6 (2.8)
Total number of glioma resections performed	
<100	61 (28.8)
100-500	100 (47.2)
>500	51 (24.1)

Table 2: Local procedures for awake mapping

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
Part 1 - Awake mapping							
Does your institute perform awake craniotomies? *n*=212	• Yes • No • No answer	97 (45.8)[a] 53 (25.0)[b] 62 (29.2)	a/b<0.0001*	5.15 (1.98-13.33)	0.0007*	1.39 (0.54-3.62)	0.4930
[Q: Insitute performs awake craniotomies: YES, *n*=97]: How is mapping performed during awake craniotomies?	• Direct electrostimulation with handheld probe • Subdural grid/strip electrodes • Both • Other	55 (56.7)[a] 2 (2.1)[b] 33 (34.0)[c] 7 (7.2)	a/b<0.0001* a/c<0.0001* b/c<0.0001*	3.03 (0.42-21.88) 1.20 (0.34-4.23) 1.60 (0.44-5.82)	0.2712 0.7764 0.4772	0.45 (0.07-2.84) 0.28 (0.099-0.77) 0.31 (0.11-0.86)	0.3992 0.0144* 0.0245*
[Q: Cortical mapping with electrostimulation with handheld probe: YES, *n*=88]: During awake craniotomy, how is cortical stimulation performed?	• Monopolar only • Bipolar only • Both • No answer	7 (8.0)[a] 49 (55.7)[b] 29 (36.4)[c] 3 (3.4)	a/b<0.0001* a/c<0.0001* b/c 0.0104*	NA 1.09 (0.31-3.83) 0.94 (0.26-3.42)	 0.8944 0.9251	NA 1.60 (0.55-4.65) 0.67 (0.23-2.01)	 0.3882 0.4802
[Q: Cortical mapping with electrostimulation with handheld probe: YES, *n*=88]: During awake craniotomy, how is subcortical stimulation performed?	• Monopolar only • Bipolar only • Both • No answer	26 (29.5)[a] 38 (47.7)[b] 18 (20.5)[c] 6 (6.8)	a/b 0.0134* a/c 0.1692 b/c 0.0001*	0.72 (0.17-3.05) 1.19 (0.31-4.60) 1.18 (0.21-6.47)	0.6597 0.8042 0.8496	0.36 (0.11-1.22) 2.19 (0.71-6.71) 1.13 (0.29-4.49)	0.1005 0.1716 0.8577
[Q: Cortical mapping with subdural grid/strip electrodes: YES, *n*=35]: What is the interelectrode space?	• 0.5 cm • 1 cm • No answer	24 (68.6)[a] 7 (20.0)[b] 4 (11.4)	a/b<0.0001*	0.87 (0.12-6.35) 1.15 (0.16-8.43)	0.8894	2.50 (0.37-16.93) 0.39 (0.06-2.70)	0.3465
What is the current range for awake cortical motor mapping? *n*=97	• Lower limit (mA) • Upper limit (mA) • I don't know/No answer	Median 2 [0-16] Median 10 [0-30] 33 (34.0)	NA	Est. 0.94 (SE=0.86) Est. 2.00 (SE=2.38)	0.285 0.4046	Est. -0.10 (SE=0.72) Est. -2.46 (SE=1.97)	0.8922 0.218

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
What are the current's increasing steps for awake cortical motor mapping? *n*=97	• 0.5 mA • 1 mA • 2 mA • Other • No answer	20 (20.6)[a] 29 (29.9)[b] 18 (18.6)[c] 3 (3.1) 27 (27.8)	a/b 0.1370 a/c 0.7264 b/c 0.0670	0.43 (0.11-1.76) 1.30 (0.31-5.41) 1.85 (0.40-8.62)	0.2426 0.7155 0.4345	0.75 (0.20-2.77) 2.81 (0.82-9.63) 0.57 (0.16-2.11)	0.6608 0.1002 0.4032
What is the stimulation frequency for awake cortical motor mapping? *n*=97	• 50 Hz • 60 Hz • Other • No answer	36 (37.1)[a] 33 (34.0)[b] 6 (6.2) 22 (22.7)	a/b 0.6528	7.97 (0.84-76.02) 0.12 (0.01-1.20)	0.0712 “	0.86 (0.23-3.17) 1.16 (0.32-4.24)	0.8256 “
What is the single pulse (phase) duration for awake cortical motor mapping? *n*=97	• 0.3 ms • 1.0 ms • Other • No answer	15 (15.5)[a] 34 (35.1)[b] 7 (7.2) 41 (42.3)	a/b 0.0017*	0.47 (0.064-3.50) 2.12 (0.29-15.72)	0.4624 “	1.06 (0.22-5.08) 0.94 (0.20-4.50)	0.9387 “
What is the train for awake cortical motor mapping? *n*=97	• 2 sec • 5 sec • Other • No answer	33 (34.0) 16 (16.5) 8 (8.2) 40 (41.2)	a/b 0.0051*	NA NA		0.87 (0.16-4.87)	0.8789
Are these stimulation settings the same for all other awake cortical mapping procedures (e.g. sensory, speech, cognition)? *n*=97	• Yes • No • No answer	49 (50.5)[a] 20 (20.6)[b] 28 (28.9)	a/b<0.0001*	1.00 (0.21-4.63)	1.00	0.42 (0.11-1.64)	0.2128
Are these stimulation settings the same for awake subcortical mapping?	• Yes • No • No answer	44 (45.4)[a] 23 (23.7)[b] 30 (30.9)	a/b 0.0015*	1.53 (0.34-6.83)	0.5777	1.54 (0.44-5.35)	0.4941

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the current range for awake cortical motor mapping?	• Lower limit (mA) • Upper limit (mA) • I don't know/No answer	Median 2.5 [0.5-16] Median 19 [2-30] 7 (30.4)	NA	NA NA		NA NA	
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What are the current's increasing steps for awake subcortical motor mapping?	• 0.5 mA • 1 mA • 2 mA • Other • No answer	7 (30.4)[a] 5 (21.7)[b] 8 (34.8)[c] 1 (4.3) 2 (8.7)	a/b 0.5061 a/c 0.7529 b/c 0.3291	NA NA NA		NA NA NA	
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the stimulation frequency for awake subcortical motor mapping?	• 50 Hz • 60 Hz • Other • No answer	8 (34.8)[a] 8 (34.8)[b] 3 (13.0) 4 (17.4)	a/b 1.0000	NA NA		NA NA	
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the single pulse (phase) duration for awake subcortical motor mapping?	• 0.3 ms • 1 ms • Other • No answer	4 (17.4)[a] 7 (40.2)[b] 4 (17.4) 8 (34.8)	a/b 0.0913	NA NA		NA NA	

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the train for awake subcortical motor mapping?	• 2 sec • 5 sec • Other • No answer	6 (26.1)[a] 6 (26.1)[b] 4 (17.4) 3 (13.0)	$_{a/b}$ 1.0000	NA NA		NA NA	
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: Are these stimulation settings the same for all other awake subcortical mapping procedures (e.g. sensory, speech, cognition)?	• Yes • No • No answer	5 (21.4)[a] 9 (39.1)[b] 9 (39.1)	$_{a/b}$ 0.1962	NA NA		NA NA	
How is motor function assessed during awake craniotomy and by whom? *n*=97	• Involuntary movement of face/arm/leg or impaired motor function during active movement of the patient, as assessed by a neurophysiologist or trained assessor	66 (68.0)[a]	$_{a/b}$<0.0001* $_{a/c}$<0.0001* $_{a/d}$<0.0001*	0.27 (0.029-2.52)	0.2503	3.55 (0.76-16.63)	0.1073
	• Involuntary movement of face/arm/leg or impaired motor function during active movement of the patient, as assessed by a non-trained assessor	12 (12.4)[b]		2.27 (0.24-21.67)	0.4750	0.50 (0.010-2.56)	0.4066
	• Involuntary movement of face/arm/leg or impaired motor function during active movement of the patient, as reported by the patient himself/herself	2 (2.1)[c]		NA		NA	
	• Motor function is not assessed during awake craniotomies	3 (3.1)[d]		NA		NA	

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
	• Other	0					
	• No answer	14 (14.4)					
Which tests are done to assess motor function during awake craniotomies? (select one or more) *n*=94	• Finger tapping	56 (59.6)[b]	a/b 0.0286	0.65 (0.20-2.16)	0.4854	2.19 (0.78-6.11)	0.1350
	• Opening and closing of hand	75 (79.8)[a]	a/c<0.0001*	0.43 (0.084-2.17)	0.3044	0.49 (0.14-1.79)	0.2814
	• Regular movement of foot	67 (71.3)[a]	b/c 0.0014*	0.61 (0.19-2.20)	0.4475	0.62 (0.21-1.83)	0.3835
	• Grasping objects	32 (34.0)[c]		0.78 (0.24-2.57)	0.6796	0.64 (0.22-1.86)	0.4174
	• Strength of hand grip	47 (50.0)[b]		2.55 (0.75-8.68)	0.1357	0.53 (0.19-1.50)	0.2313
	• Other	5 (5.3)					
How is language function assessed during awake craniotomy and by whom? *n*=97	• Stimulation-induced anomia, alexia or speech arrest as assessed by a neuro-linguist or a trained assessor	67 (69.1)[a]	a/b<0.0001* a/c<0.0001* b/c 0.0170	0.39 (0.036-4.28)	0.4431	NA	
	• Stimulation induced anomia, alexia or speech arrest, as assessed by a non-trained assessor	8 (8.2)[b]		NA		NA	
	• Stimulation-induced anomia, alexia or speech arrest, as reported by the patient himself/herself	1 (1.0)[c]		NA		NA	
	• No answer	19 (19.6)					

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
Which tests are done to assess language function during awake craniotomies? (select one or more) *n*=97	• Spontaneous speech production	76 (78.4)[a]	$_{a/b}$ 0.0045*	0.56 (0.14-2.28)	0.4207	0.67 (0.21-2.11)	0.4956
	• Reading	50 (51.5)[b]	$_{a/c}$<0.0001*	1.40 (0.44-4.43)	0.5611	1.87 (0.68-5.11)	0.2221
	• Writing	15 (15.5)[c]	$_{b/c}$ 0.0004*	0.80 (0.18-3.50)	0.7681	1.28 (0.33-4.96)	0.7158
	• Counting	70 (72.2)[a]		1.03 (0.30-3.51)	0.9615	1.27 (0.44-3.69)	0.6615
	• Repetition	57 (58.8)[b]		0.92 (0.29-2.95)	0.8846	0.85 (0.31-2.35)	0.7572
	• Semantic associations	36 (37.1)[c]		1.26 (0.39-4.03)	0.7004	1.43 (0.52-3.92)	0.4884
	• Word fluency	52 (53.6)[b]		0.92 (0.29-2.88)	0.8857	0.94 (0.45-2.54)	0.9034
	• Verb generation	27 (27.8)[c]		3.83 (0.78-18.87)	0.0990	1.31 (0.43-4.00)	0.6365
	• Object picture naming (e.g. Boston naming test)	70 (72.2)[a]		0.65 (0.16-2.73)	0.5607	0.36 (0.10-1.26)	0.1105
	• Word and sentence comprehension (e.g. Token test)	29 (29.9)[c]		1.64 (0.45-5.95)	0.4520	0.64 (0.22-1.84)	0.4046
	• Other	0					
How is sensory function assessed during awake craniotomies? *n*=97	• Stimulation-induced focal paresthesia of the face/trunk/arm/leg during application of the stimulus as reported by the patient himself/herself	65 (67.0)	NA	NA		NA	
	• Other	4 (6.0)					
	• No answer	28 (28.9)					
How is cognitive function assessed during awake craniotomies and by whom? *n*=97	• Diminished performance in cognitive function testing, as assessed by a neuro-psychologist or trained assessor	44 (45.4)[a]	$_{a/b}$<0.0001* $_{a/c}$ 0.0009* $_{b/c}$<0.0001*	0.82 (0.15-4.32)	0.8105	4.03 (1.13-14.31)	0.0313*
	• Diminished performance in cognitive function testing, as assessed by a non-trained assessor	2 (2.1)[b]		NA		NA	

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
	• Cognitive functions are not assessed	22 (22.7)[c]		NA		NA	
	• Other	0					
	• No answer	29 (29.9)					
Which cognitive domains are subject to testing? *n*=44	• Visuospatial	31 (70.5)[a]	a/b<0.0001*	0.85 (0.26-2.80)	0.7874	2.24 (0.76-6.58)	0.1411
	• Memory	38 (86.4)[a]	a/c<0.0001*	1.42 (0.42-4.74)	0.5710	1.35 (0.48-3.79)	0.5672
	• Calculation	44 (100.0)[a]	b/c 0.0004*	0.69 (0.22-2.24)	0.5432	2.42 (0.86-6.80)	0.0922
	• Emotions (e.g. FEEST)	12 (27.3)[c]		1.09 (0.20-5.94)	0.9190	1.44 (0.33-6.40)	0.6293
	• Face recognition	22 (50.0)[b]		0.72 (0.18-2.84)	0.6393	3.68 (0.92-14.83)	0.0664
	• Executive functions (e.g. Stroop test, no-go test)	19 (43.2)[b]		1.34 (0.31-5.73)	0.6928	3.91 (0.99-15.50)	0.0522
	• Music	10 (22.7)[c]		0.65 (0.11-3.95)	0.6428	4.95 (0.55-44.39)	0.1527
	• Other	0					
Is awake mapping combined with asleep mapping during the same resection? *n*=97	• Always	9 (9.3)[a]	a/b 0.1357	1.92 (0.15-24.66)	0.6149	0.59 (0.048-7.41)	0.6859
	• Usually (>50% of cases)	16 (16.5)[b]	a/c 0.0044*	0.77 (0.16-3.60)	0.7392	0.89 (0.23-3.47)	0.8855
	• Sometimes (<50% of cases)	24 (24.7)[c]	a/d 0.0005*	1.50 (0.34-6.60)	0.5930	1.46 (0.43-4.92)	0.5422
	• Never	28 (28.9)[d]	b/c 0.1590	1.01 (0.26-3.83)	1.0000	0.69 (0.22-2.17)	0.5295
	• No answer	20 (20.6)	b/d 0.0398				
			c/d 0.5101				
Are surgical adjuncts or additional (intraoperative) imaging modalities used during awake craniotomy? (select one or more answers) *n*=97	• Fluorescence/5-ALA	46 (47.4)[b]	a/b<0.0001*	1.21 (0.36-3.98)	0.7590	3.77 (1.33-10.66)	0.0124*
	• Intraoperative MRI	19 (19.6)[c]	a/c<0.0001*	5.48 (0.62-48.77)	0.1342	0.23 (0.059-0.90)	0.0343*
	• Intraoperative ultrasound	49 (50.5)[a]	b/c 0.0170	1.16 (0.38-3.62)	0.7920	1.07 (0.40-2.87)	0.8956
	• Diffusion tensor imaging	55 (56.7)[a]		0.83 (0.26-2.65)	0.7507	1.01 (0.37-2.74)	0.9918
	• Functional MRI	40 (41.2)[b]		0.69 (0.22-2.17)	0.5311	0.69 (0.25-1.89)	0.4749
	• Other	7 (7.2)					
	• None	5 (5.2)					

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
Are ECoG or intraoperative EEG used during awake craniotomy? *n*=97	• ECoG only	21 (21.6)[a]	a/b 0.0005*	1.23 (0.22-6.98)	0.8186	1.16 (0.31-4.40)	0.8276
	• EEG only	6 (6.2)[b]		0.42 (0.063-2.80)	0.3705	0.85 (0.15-4.86)	0.8552
	• Both	9 (9.3)[b]		1.40 (0.14-14.29)	0.7757	0.34 (0.056-2.12)	0.2506
	• None	30 (30.9)[a]		1.18 (0.27-5.17)	0.8238	1.53 (0.48-4.92)	0.4711
	• No answer	31 (32.0)					
[Q: ECoG and/or intraoperative EEG used: YES, *n*=36]: Are ECoG and/or EEG used to record focal after-discharge seizures or to resect the epileptic focus?	• To record after-discharge seizures	8 (22.2)[a]	a/b 1.0000	NA		NA	
	• To resect the epileptic focus	8 (22.2)[b]	a/c 0.0011*	NA		NA	
	• Both	16 (44.4)[c]	b/c 0.0011*	NA		NA	
	• None	4 (11.1)		NA		NA	
Which anesthesia technique(s) is/are used for awake craniotomy? (select one or more answers) *n*=97	• Asleep with protected airway using endotracheal tube (ETT) – awake – re-intubation (classic asleep-awake-asleep technique)	10 (10.3)[a]	a/b<0.0001* a/c<0.0001* b/c 0.7769	0.58 (0.089-3.72)	0.5632	NA	
	• Asleep with protected airway using laryngeal mask airway (LMA) – awake – moderate sedation (adjusted asleep-awake-asleep technique)	40 (41.2)[b]		2.09 (0.61-7.14)	0.2379	0.48 (0.17-1.33)	0.1589
	• Moderate sedation – awake – moderate sedation (awake-awake-awake technique)	38 (39.2)[c]		0.35 (0.11-1.15)	0.0837	0.45 (0.16-1.29)	0.1357
	• Other	3 (3.1)					
	• No answer	12 (12.4)					

Table 2: Local procedures for awake mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted odds ratio for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted odds ratio for European vs. US neurosurgeons (95% CI)	*P* value
Which drug combinations are used for anesthesia for awake craniotomy? (select one or more answers) *n*=97	• Propofol/remifentanil	38 (39.2)[a]	$_{a/b}$<0.0001*	2.02 (0.58-7.07)	0.2728	3.97 (1.35-11.70)	0.0124*
	• Propofol/remifentanil/ dexmedetomidine	40 (41.2)[a]	$_{a/c}$<0.0001* $_{b/c}$ 0.0276	0.46 (0.13-1.65)	0.2334	0.15 (0.050-0.48)	0.0012*
	• Dexmedetomidine	11 (11.3)[b]		1.64 (0.16-16.72)	0.6778	0.14 (0.15-1.39)	0.0941
	• Volatile anesthetic (in the case of LMA)	3 (3.1)[c]		NA		0.60 (0.035-10.20)	0.7238
	• Other	1 (1.0)		NA		NA	
	• No answer	16 (16.5)					

Table 3: Local procedures for asleep mapping

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
Part 2 - Asleep mapping							
Does your insitute perform asleep mapping techniques? *n*=212	• Yes • No • No answer	77 (36.3)[a] 63 (29.7)[b] 72 (34.0)	a/b 0.1489	3.56 (1.36-9.26)	0.0094*	0.39 (0.15-1.00)	0.0511
[Q: Insitute performs asleep mapping: YES, *n*=77]: During asleep mapping, is cortical stimulation performed with a monopolar or bipolar stimulator?	• Monopolar • Bipolar • Both • No answer	18 (23.4)[a] 23 (29.9)[b] 28 (36.4)[c] 8 (10.4)	a/b 0.3632 a/c 0.0791 b/c 0.3931	0.94 (0.23-3.90) 1.13 (0.27-4.72) 0.95 (0.26-3.47)	0.9309 0.8695 0.7096	0.24 (0.053-1.044) 2.79 (0.74-10.58) 1.26 (0.37-4.26)	0.0571 0.1309 0.7096
During asleep mapping, is subcortical stimulation performed with a monopolar or bipolar stimulator? *n*=77	• Monopolar • Bipolar • Both • No answer	31 (40.3)[a] 19 (24.7)[b] 12 (15.6)[c] 15 (19.5)	a/b 0.0394 a/c 0.0007* b/c 0.1606	1.61 (0.38-6.78) 0.40 (0.09-1.76) 1.65 (0.29-9.37)	0.5185 0.2263 0.5726	0.59 (0.17-2.09) 2.01 (0.51-7.99) 0.91 (0.22-3.82)	0.4169 0.3214 0.8976
Are the stimulation settings for asleep mapping the same as for mapping during awake craniotomy? *n*=77	• Yes • No • No answer	37 (48.1)[a] 18 (23.4)[b] 22 (28.6)	a/b 0.0014*	1.18 (0.26-5.34)	0.8312	1.40 (0.25-5.54)	0.6343
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO, *n*=18]: What is the current range for asleep cortical motor mapping?	• Lower limit • Upper limit • I don't know/No answer	Median 2 [1-8] Median 12 [6-30] 7 (38.9)	NA	NA NA		NA NA	

Table 3: Local procedures for asleep mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO, *n*=18]: What are the current's increasing steps for asleep cortical motor mapping?	• 0.5 mA • 1 mA • 2 mA • Other • No answer	3 (16.7)[a] 4 (22.2)[b] 5 (27.8)[c] 1 (5.6) 5 (27.8)	a/b 0.6811 a/c 0.4299 b/c 0.7021	NA NA NA		NA NA NA	
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO]: What is the stimulation frequency for asleep cortical motor mapping?	• 50 Hz • 60 Hz • No answer	6 (33.3)[a] 7 (38.9)[b] 5 (27.8)	a/b 0.7302	NA NA		NA NA	
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: What is the single pulse (phase) duration for asleep cortical motor mapping?	• 0.3 ms • 1 ms • Other • No answer	3 (16.7)[a] 7 (38.9)[b] 2 (11.1) 6 (33.3)	a/b 0.1427	NA NA		NA NA	
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: What is the train for asleep cortical motor mapping?	• 2 sec • 5 sec • Other • No answer	7 (38.9)[a] 2 (11.1)[b] 2 (11.1) 7 (38.9)	a/b 0.0576	NA NA		NA NA	

Table 3: Local procedures for asleep mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: Are these stimulation settings the same for all other asleep cortical mapping procedures (e.g. sensory, speech, cognition)?	• Yes • No • No answer	6 (33.3)[a] 2 (11.1)[b] 10 (55.6)	[a/b] 0.1141	NA NA		NA NA	
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: Are these stimulation settings the same for asleep subcortical mapping?	• Yes • No • No answer	5 (27.8)[a] 5 (27.8)[b] 8 (44.4)	[a/b] 1.0000	NA NA		NA NA	
Is continuous dynamic mapping used for asleep mapping (integrated monopolar with suction probe/ ultrasonic aspirator)? *n*=77	• Yes • No • No answer	23 (29.9)[a] 39 (50.6)[b] 15 (19.5)	[a/b] 0.0090*	2.19 (0.35-13.57)	0.4012	6.26 (1.18-37.10)	0.0314*
Is transcortical magnetic stimulation (TMS) used for asleep mapping? *n*=77	• Yes • No • No answer	5 (6.5) 58 (75.3) 14 (18.2)	[a/b]<0.0001*	NA		NA	

Table 3: Local procedures for asleep mapping (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
How are eloquent areas identified during asleep mapping? (select one or more answers) *n*=77	• SSEPs (somato-sensory evoked potentials)	50 (64.9)[a]	a/b<0.0001*	0.75 (0.22-2.58)	0.6545	0.74 (0.24-2.25)	0.5948
	• MEPs (motor evoked potentials)	61 (79.2)[a]		0.13 (0.15-1.11)	0.0622	1.44 (0.38-5.41)	0.5921
	• CMAPs (compound motor action potentials)	11 (14.3)[b]		6.14 (0.66-57.31)	0.1111	0.17 (0.03-1.00)	0.0493*
	• ADPs (after-discharge potentials)	10 (13.0)[b]		0.97 (0.19-5.02)	0.9664	0.13 (0.014-1.13)	0.0646
	• Phase reversal	40 (51.9)[a]		0.39 (0.10-1.47)	0.1620	0.21 (0.062-0.69)	0.0103*
	• Other	2 (2.6)					
Is a clinical neurophysiologist present and is telemetric monitoring used during asleep mapping? *n*=77	• Yes, with telemetric monitoring	30 (39.0)[a]	a/b 0.1739	6.00 (1.22-29.60)	0.0278*	0.11 (0.025-0.52)	0.0049*
	• Yes, without telemetric monitoring	22 (28.6)[b]	a/c 0.0577	0.67 (0.12-3.63)	0.6428	5.91 (1.01-34.56)	0.0485*
	• Neurophysiologist is not present	19 (24.7)[c]	b/c 0.5854	0.26 (0.065-1.05)	0.0589	2.58 (0.66-10.086)	0.1731
	• No answer	6 (7.8)					
Are surgical adjuncts or additional (intraoperative) imaging modalities used during asleep mapping? (select one or more answers) *n*=77	• Fluorescence/5-ALA	37 (48.1)[a]	a/b<0.1259	1.13 (0.33-3.87)	0.8406	2.26 (0.73-6.98)	0.1547
	• Intraoperative MRI	17 (22.1)[c]	a/c<0.0001*	5.62 (0.63-50.56)	0.1234	0.53 (0.12-2.28)	0.3956
	• Intraoperative ultrasound	44 (57.1)[a]	b/c 0.0096*	0.83 (0.24-2.79)	0.7580	1.56 (0.51-4.76)	0.4374
	• Diffusion tensor imaging (DTI)	43 (55.8)[a]		1.40 (0.42-4.70)	0.5823	0.86 (0.29-2.62)	0.7962
	• Functional MRI (fMRI)	32 (41.6)[b]		1.33 (0.38-4.64)	0.6571	0.51 (0.16-1.62)	0.2566
	• None	3 (3.9)					
Are ECoG or intraoperative EEG used during asleep mapping? *n*=77	• ECoG only	13 (16.9)[a]	a/b 0.1514	0.46 (0.076-2.79)	0.3995	1.18 (0.20-7.14)	0.8561
	• EEG only	7 (9.1)[b]	a/c<0.8326	2.20 (0.21-22.74)	0.5069	1.39 (0.20-9.72)	0.7430
	• Both	14 (18.2)[c]	b/c 0.1011	0.94 (0.20-4.40)	0.9371	0.33 (0.070-1.58)	0.1665
	• None	25 (32.5)[d]	b/d 0.0004*	1.18 (0.31-4.54)	0.8099	1.78 (0.49-6.40)	0.3802
	• No answer	18 (23.4)					
How is general anethesia induced? *n*=77	• Total Intravenous Anesthesia (TIVA)	48 (62.3)[a]	a/b<0.0001*	0.39 (0.080-1.87)	0.2373	2.19 (0.53-9.045)	0.2771
	• Volatile anesthetic	5 (6.5)[b]	a/c<0.0001*	NA		1.15 (0.16-8.27)	0.8868
	• Combination of both	12 (15.6)[c]	b/c 0.0726	1.10 (0.20-5.92)	0.9134	0.29 (0.048-1.73)	0.1742
	• Other	12 (15.6)					

Table 4: Local procedures for assessing neurological morbidity

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US centers (95% CI)	*P* value
Part 3 – Neurological morbidity							
How is neurological morbidity assessed at your institute? (select one or more answers) *n*=138	• NIHSS (Neurological Institute of Health Stroke Scale)	31 (22.5)[b]	$_{a/b}$<0.0001* $_{a/c}$<0.0001*	0.96 (0.36-2.55)	0.9342	0.50 (0.19-1.33)	0.1642
	• NIS (Neurological Impairment Scale)	15 (10.9)[c]	$_{b/c}$ 0.0031*	0.71 (0.21-2.42)	0.5797	1.17 (0.34-4.00)	0.8063
	• NANO (Neurologic Assessment in Neuro-Oncology)	10 (7.2)[c]		NA		3.06 (0.33-28.26)	0.3232
	• Free text in electronic patient system	107 (77.5)[a]		0.50 (0.17-1.50)	0.2142	1.23 (0.44-3.41)	0.6952
	• Other	3 (2.2)					
	• No answer	7 (5.1)					
How would you preferably assess neurological morbidity for research purposes? *n*=138	• Standardized scale (e.g., NIHSS, NIS, NANO)	85 (61.6)[a]	$_{a/b}$<0.0001*	1.59 (0.59-4.27)	0.3591	1.39 (0.52-3.73)	0.5117
	• Free text in electronic patient system	38 (27.5)[b]		0.63 (0.23-1.69)	0.3591	0.72 (0.27-1.93)	0.5117
	• Other	1 (0.72)					
	• No answer	14 (10.1)					
Who assesses postoperative neurological morbidity at your institute? (select one or more answers) *n*=138	• Neurosurgeon	127 (92.0)	NA	1.02 (0.20-5.16)	0.9853	1.53 (0.30-7.72)	0.6090
	• Neurologist	41 (29.7)		0.87 (0.37-2.08)	0.7550	0.87 (0.37-2.08)	0.7550
	• Oncologist	19 (13.8)		2.12 (0.59-7.60)	0.2493	0.85 (0.27-2.70)	0.7774
	• Resident	56 (40.6)		3.88 (1.49-10.08)	0.0054*	0.98 (0.40-2.42)	0.9667
	• Physician Assistant	35 (25.4)		0.51 (0.20-1.31)	0.1608	1.28 (0.50-3.29)	0.6064
	• Nurse Practitioner	22 (15.9)		1.49 (0.48-4.59)	0.4858	0.15 (0.44-0.53)	0.0032*
	• Intern	6 (4.3)		1.59 (0.15-17.18)	0.7031	2.48 (0.23-26.67)	0.4526
	• Study Nurse	7 (5.1)		NA		2.38 (0.25-22.84)	0.4539
	• Other	2 (1.4)					
	• No answer	5 (3.6)					

Table 5: Local procedures for perioperative decision making

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
Part 4 – Decision making							
Which of the following are reasons at your institute to choose for awake craniotomy for a specific case? (select one or more answers) *n*=121	• The possibility to perform awake mapping or monitoring	68 (56.2)[a]	$_{a/b}$<0.0001* $_{a/c}$<0.0001*	0.72 (0.13-3.97)	0.7092	0.72 (0.16-3.28)	0.6753
	• When mapping is preferred, awake is the only option at our center	3 (2.5)[c]	$_{b/c}$ 0.0687	NA		NA	
	• Anesthesia risks	9 (7.4)[b]		0.80 (0.13-4.95)	0.8100	0.66 (0.12-3.66)	0.6363
	• The ability for the patient to go home the same day	1 (0.83)[c]		NA		NA	
	• Strong wish of the patient	7 (5.8)[b]		NA		NA	
	• Other	9 (7.4)[b]		NA		NA	
	• None of the above	26 (21.5)		NA		NA	
	• No answer	30 (24.8)		NA		NA	

Table 5: Local procedures for perioperative decision making (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
Which information regarding the mapping procedure is documented at your institution? (select one or more answers) *n*=121	• Digital photography of the operative field with labeled mapping sites	31 (25.6)	NA	1.24 (0.36-4.27)	0.7284	3.62 (1.03-12.69)	0.0441*
	• Digital video recording of the view through the operation microscope during the mapping procedure	28 (23.1)		2.48 (0.59-10.27)	0.2100	4.40 (1.10-17.56)	0.0357*
	• Screenshots of the view through the operation microscope during the mapping procedure	31 (25.6)		0.65 (1.31-4.16)	0.6494	2.56 (0.83-7.86)	0.1005
	• Digital video recording of the patient's task performance during the mapping procedure	7 (5.8)		NA	0.8471	0.84 (0.13-5.64)	0.8576
	• The stimulation threshold and intensity in relation with eloquent mapping sites	48 (39.7)		0.90 (0.32-2.57)	0.9182	0.64 (0.24-1.74)	0.3822
	• Information regarding the evoked potentials	34 (28.1)		1.06 (0.35-3.25)	0.2074	0.73 (0.25-2.10)	0.5543
	• Information regarding the neuronavigation (e.g., screenshots and coordinates)	36 (29.8)		2.10 (0.66-6.63)		0.54 (0.19-1.54)	0.2490
	• ECoG information	24 (19.8)		2.47 (0.63-8.91)	0.1999	0.35 (0.11-1.12)	0.0764
	• EEG information	13 (10.7)		2.73 (0.50-14.81)	0.2440	0.37 (0.089-1.50)	0.1632
	• Other	3 (2.5)					
	• None of the above	10 (8.3)					
	• No answer	26 (21.5)					

Table 5: Local procedures for perioperative decision making (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
On which information is your decision to end the resection based? (1-10 for each answer, 1 meaning not important at all and 10 meaning extremely important) *n*=121	• The patient's task performance, which decreases significantly during awake craniotomy and suggests that maximum safe resection is reached	Median 10 [1-10]	NA	Est. 0.79 (SE=0.65)	0.2294	Est. 0.37 (SE=0.62)	0.5551
	• The evoked potentials, which show that the amplitude diminishes significantly and suggests that maximum safe resection is reached	Median 9 [1-10]		Est. -0.46 (SE=0.67)	0.4909	Est. 0.67 (SE=0.65)	0.3089
	• The imaging, which suggests that maximum safe resection is reached (based on either the neuronavigation, DTI, fMRI or ioMRI)	Median 8 [1-10]		Est -1.28 (SE=0.61)	0.0406*	Est. -0.47 (SE=0.60)	0.4396
	• The macroscopy, which indicates a gross-total resection (GTR) and suggests that a maximum macroscopic resection is reached (based on either your expertise or 5-ALA)	Median 8 [1-10]		Est. 0.12 (SE=0.58)	0.8423	Est. -0.65 (SE=0.57)	0.2648
	• None of the above	2 (1.7)					
	• No answer	10 (8.3)					
How are initial stimulation-induced seizures suppressed? (select one or more answers) *n*=121	• Irrigating the exposed brain surface with chilled sodiumchloride solution	46 (38.0)[a]	a/b 0.0388 a/c 0.0120*	0.80 (0.25-2.53)	0.7173	0.52 (0.18-1.54)	0.2362
	• Irrigating the exposed brain surface with chilled Ringer's lactate solution	31 (25.6)[b]	b/c 0.6512	0.80 (0.23-2.59)	0.7032	1.80 (0.61-5.33)	0.2896
	• Administration of anti-epileptic medication	28 (23.1)[c]		0.71 (0.21-2.43)	0.5861	1.83 (0.57-5.93)	0.3132
	• Other	2 (1.7)					
	• None of the above	5 (4.1)					
	• No answer	31 (25.6)					

Table 5: Local procedures for perioperative decision making (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
How are recurrent stimulation-induced seizures treated? (select one or more answers) *n*=121	• Irrigating the exposed brain surface with chilled sodiumchloride solution	42 (34.7)[a]	$_{a/b}$ 0.0470 $_{ab/c}$ 0.0271*	1.18 (0.36-3.86)	0.7792	0.63 (0.21-1.85)	0.3987
	• Irrigating the exposed brain surface with chilled Ringer's lactate solution	28 (23.1)[b]	$_{ab/d}$ 0.2045 $_{ab/e}$ 0.0001*	1.23 (0.37-4.07)	0.7396	1.63 (0.54-4.89)	0.3829
	• Administration of anti-epileptic medication	53 (43.8)[c]	$_{ab/f}$<0.0001*	0.35 (0.084-1.42)	0.1413	0.55 (0.17-1.78)	0.3170
	• Administration of intravenous propofol	37 (30.6)[d]	$_{c/d}$ 0.0340	0.40 (0.12-1.34)	0.1380	1.46 (0.47-4.39)	0.4993
	• Administration of intravenous benzodiazepines	19 (15.7)[e]	$_{c/e}$ <0.0001*	1.22 (0.32-4.74)	0.7714	0.47 (0.14-1.59)	0.2264
	• The mapping procedure is replaced by asleep mapping and the resection is continued	14 (11.6)[f]	$_{c/f}$ <0.0001* $_{d/e}$ 0.0061	0.25 (0.049-1.32)	0.1030	0.53 (0.10-2.76)	0.4494
	• The mapping procedure is definitively terminated and the resection is continued under general anesthesia	13 (10.7)[f]	$_{d/f}$ 0.0002* $_{e/f}$ 0.3014	0.89 (0.20-4.01)	0.8778	1.03 (0.25-4.20)	0.9652
	• Other	3 (2.5					
	• None of the above	6 (5.0)					
	• No answer	30 (24.8)					

Table 6: Procedural preferences for awake mapping specified by surgeon's experience

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
Part 1 - Awake mapping					
[Q: Insitute performs awake craniotomies: YES, *n*=97]: How is mapping performed during awake craniotomies?	• Direct electrostimulation with handheld probe • Subdural grid/strip electrodes • Both • Other	16 (72.7) 4 (18.2) 2 (9.1) 0	26 (65.0) 0 12 (30.0) 2 (5.0)	13 (37.1) 1 (2.9) 19 (54.3) 2 (5.7)	0.0009*
[Q: Cortical mapping with electrostimulation with handheld probe: YES, *n*=88]: During awake craniotomy, how is cortical stimulation performed?	• Monopolar only • Bipolar only • Both • No answer	2 (11.1) 10 (55.6) 4 (22.2) 2 (11.1)	5 (13.2) 20 (52.6) 12 (31.6) 1 (2.6)	0 19 (59.4) 13 (40.6) 0	0.5389
[Q: Cortical mapping with electrostimulation with handheld probe: YES, *n*=88]: During awake craniotomy, how is subcortical stimulation performed?	• Monopolar only • Bipolar only • Both • No answer	6 (33.3) 7 (38.9) 2 (11.1) 3 (16.7)	11 (28.9 19 (50.0) 6 (15.8) 2 (5.3)	9 (28.1) 12 (37.5) 10 (31.3) 1 (3.1)	0.4646
[Q: Cortical mapping with subdural grid/strip electrodes: YES, *n*=35]: What is the interelectrode space?	• 0.5 cm • 1 cm • No answer	2 (66.7) 1 (33.3) 0	9 (75.0) 2 (16.7) 1 (8.3)	4 (20.0) 13 (65.0) 3 (15.0)	0.0085*
What is the current range for awake cortical motor mapping? *n*=97	• Lower limit (mA) • Upper limit (mA) • I don't know/No answer	Median 1 [0-5.5] Median 4.5 [0-22] 9 (40.9)	Median 2 [0-12.5] Median 10 [0-30] 13 (32.6)	Median 2 [0.5-16] Median 10 [3.5-26] 7 (20.0)	NA
What are the current's increasing steps for awake cortical motor mapping? *n*=97	• 0.5 mA • 1 mA • 2 mA • Other • No answer	2 (9.1) 4 (18.2) 4 (18.2) 3 (13.6) 9 (40.9)	8 (20.0) 8 (20.0) 7 (17.5) 6 (15.0) 11 (27.5)	9 (25.7) 9 (25.7) 7 (20.0) 3 (8.6) 7 (20.0)	0.9106

Table 6: Procedural preferences for awake mapping specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
What is the stimulation frequency for awake cortical motor mapping? *n*=97	• 50 Hz • 60 Hz • Other • No answer	6 (27.3) 3 (13.6) 1 (4.5) 12 (54.5)	15 (37.5) 8 (20.0) 3 (7.5) 14 (35.0)	15 (42.9) 12 (34.3) 2 (5.7) 6 (17.1)	0.7298
What is the single pulse (phase) duration for awake cortical motor mapping? *n*=97	• 0.3 ms • 1.0 ms • Other • No answer	2 (9.1) 6 (27.3) 1 (4.5) 13 (59.1)	8 (20.0) 13 (32.5) 3 (7.5) 16 (40.0)	5 (14.3) 15 (42.9) 4 (11.4) 11 (31.4)	0.6161
What is the train for awake cortical motor mapping? *n*=97	• 2 sec • 5 sec • Other • No answer	6 (27.3) 4 (18.2) 0 12 (54.5)	12 (30.0) 6 (15.0) 6 (15.0) 16 (40.0)	15 (42.9) 6 (17.1) 2 (5.7) 12 (34.4)	0.8153
Are these stimulation settings the same for all other awake cortical mapping procedures (e.g. sensory, speech, cognition)? *n*=97	• Yes • No • No answer	10 (45.5) 1 (4.5) 11 (50.0)	20 (50.0) 10 (25.0) 10 (25.0)	19 (54.3) 9 (25.7) 7 (20.0)	0.2828
Are these stimulation settings the same for awake subcortical mapping?	• Yes • No • No answer	8 (36.4) 0 14 (63.6)	19 (47.5) 9 (22.5) 12 (30.0)	16 (45.7) 14 (40.0) 5 (14.3)	0.1293
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the current range for awake cortical motor mapping?	• Lower limit (mA) • Upper limit (mA) • I don't know/No answer	NA	Median 2 [0.5-5] Median 11 [4-20] 3 (37.5)	Median 4.5 [1-15.5] Median 20 [2-30] 4 (28.6)	NA
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What are the current's increasing steps for awake subcortical motor mapping?	• 0.5 mA • 1 mA • 2 mA • Other • No answer	NA	0 1 (12.5) 4 (50.0) 3 (37.5) 1 (12.5)	4 (28.6) 3 (21.4) 4 (28.6) 3 (21.4) 0	NA

Table 6: Procedural preferences for awake mapping specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the stimulation frequency for awake subcortical motor mapping?	• 50 Hz • 60 Hz • Other • No answer	NA	2 (22.2) 4 (44.4) 2 (22.2) 1 (11.1)	6 (42.9) 3 (21.4) 2 (14.3) 3 (21.4)	NA
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the single pulse (phase) duration for awake subcortical motor mapping?	• 0.3 ms • 1 ms • Other • No answer	NA	2 (22.2) 2 (22.2) 3 (33.3) 2 (22.2)	2 (14.3) 5 (35.7) 1 (7.1) 7 (50.0)	NA
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: What is the train for awake subcortical motor mapping?	• 2 sec • 5 sec • Other • No answer	NA	3 (33.3) 1 (11.1) 2 (22.2) 3 (33.3)	3 (21.4) 5 (35.7) 2 (14.3) 4 (28.6)	NA
[Q: Stimulation settings the same for awake subcortical mapping: NO, *n*=23]: Are these stimulation settings the same for all other awake subcortical mapping procedures (e.g. sensory, speech, cognition)?	• Yes • No • No answer	NA	1 (11.1) 2 (22.2) 6 (66.6)	2 (14.3) 5 (35.7) 7 (50.0)	NA
Is awake mapping combined with asleep mapping during the same resection? *n*=97	• Always • Usually (>50% of cases) • Sometimes (<50% of cases) • Never • No answer	1 (4.5) 0 8 (36.4) 7 (31.8) 6 (27.3)	3 (7.5) 6 (15.0) 7 (17.5) 14 (35.0) 10 (25.0)	5 (14.3) 9 (25.7) 9 (25.7) 7 (20.0) 5 (14.3)	0.1963

Table 6: Procedural preferences for awake mapping specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
Are surgical adjuncts or additional (intraoperative) imaging modalities used during awake craniotomy? (select one or more answers) *n*=97	• Fluorescence/5-ALA	11 (50.0)	19 (47.5)	19 (54.3)	0.9448
	• Intraoperative MRI	2 (11.1)	7 (17.5)	10 (28.6)	
	• Intraoperative ultrasound	13 (59.1)	16 (40.0)	20 (57.1)	
	• Diffusion tensor imaging	13 (59.1)	18 (45.0)	24 (68.6)	
	• Functional MRI	8 (36.4)	15 (37.5)	17 (48.6)	
	• Other	0	0	1 (2.9)	
	• None	1 (4.5)	5 (12.5)	0	
Are ECoG or intraoperative EEG used during awake craniotomy? *n*=97	• ECoG only	5 (22.7)	7 (17.5)	9 (25.7)	0.8191
	• EEG only	0	2 (5.0)	4 (11.4)	
	• Both	1 (4.5)	4 (10.0)	4 (11.4)	
	• None	10 (45.5)	9 (22.5)	11 (31.4)	
	• No answer	6 (27.3)	18 (45.0)	7 (20.0)	
[Q: ECoG and/or intraoperative EEG used: YES, *n*=36]: Are ECoG and/or EEG used to record focal after-discharge seizures or to resect the epileptic focus?	• To record after-discharge seizures	1 (16.7)	2 (15.4)	5 (29.4)	0.8929
	• To resect the epileptic focus	2 (33.3)	2 (15.4)	4 (23.5)	
	• Both	3 (66.7)	6 (46.2)	7 (41.2)	
	• None	0	3 (23.1)	1 (5.9)	

Table 7: Procedural preferences for asleep mapping specified by surgeon's experience

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
Part 2 - Asleep mapping					
[Q: Insitute performs asleep mapping: YES, *n*=77]: During asleep mapping, is cortical stimulation performed with a monopolar or bipolar stimulator?	• Monopolar • Bipolar • Both • No answer	5 (21.7) 8 (34.8) 8 (34.8) 2 (8.7)	5 (20.0) 10 (40.0) 8 (32.0) 2 (8.0)	8 (27.6) 5 (17.2) 12 (41.4) 4 (13.8)	0.5103
During asleep mapping, is subcortical stimulation performed with a monopolar or bipolar stimulator? *n*=77	• Monopolar • Bipolar • Both • No answer	9 (39.1) 7 (30.4) 3 (13.0) 4 (17.4)	10 (40.0) 8 (32.0) 4 (16.0) 3 (12.0)	12 (41.4) 4 (13.8) 8 (27.6) 5 (17.2)	0.4212
Are the stimulation settings for asleep mapping the same as for mapping during awake craniotomy? *n*=77	• Yes • No • No answer	12 (52.2) 1 (4.3) 10 (43.5)	11 (44.0) 8 (32.0) 6 (24.0)	14 (48.3) 9 (31.0) 6 (20.7)	0.08681
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO, *n*=18]: What is the current range for asleep cortical motor mapping?	• Lower limit • Upper limit • I don't know/No answer	0 0 1 (100.0)	Median 1.5 [0-4] Median 8 [0-30] 2 (25.0)	Median 2.5 [1-8] Median 11 [6-30] 3 (33.3)	NA
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO, *n*=18]: What are the current's increasing steps for asleep cortical motor mapping?	• 0.5 mA • 1 mA • 2 mA • Other • No answer	0 0 1 (100.0) 0 0	1 (12.5) 0 2 (25.0) 2 (25.0) 3 (37.5)	2 (22.2) 2 (22.2) 2 (22.2) 1 (11.1) 2 (22.2)	NA
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO, *n*=18]:]: What is the stimulation frequency for asleep cortical motor mapping?	• 50 Hz • 60 Hz • No answer	1 (100.0) 0 0	2 (25.0) 3 (37.5) 3 (37.5)	3 (33.3) 4 (44.4) 2 (22.2)	NA

Table 7: Procedural preferences for asleep mapping specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: What is the single pulse (phase) duration for asleep cortical motor mapping?	• 0.3 ms • 1 ms • Other • No answer	0 1 (100.0) 0 0	0 4 (50.0) 1 (25.0) 3 (37.5)	3 (33.3) 2 (22.2) 1 (11.1) 3 (33.3)	NA
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: What is the train for asleep cortical motor mapping?	• 2 sec • 5 sec • Other • No answer	1 (100.0) 0 0 0	3 (37.5) 1 (12.5) 1 (12.5) 3 (37.5)	3 (33.3) 1 (11.1) 1 (11.1) 4 (44.4)	NA
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: Are these stimulation settings the same for all other asleep cortical mapping procedures (e.g. sensory, speech, cognition)?	• Yes • No • No answer	0 0 1 (100.0)	3 (37.5) 1 (12.5) 4 (50.0)	3 (33.3) 1 (11.1) 5 (55.5)	NA
[Q: Stimulation settings for asleep mapping the same as for awake mapping: NO *n*=18]: Are these stimulation settings the same for asleep subcortical mapping?	• Yes • No • No answer	0 0 1 (100.0)	3 (37.5) 1 (12.5) 4 (50.0)	2 (22.2) 4 (44.4) 3 (33.3)	NA
Is continuous dynamic mapping used for asleep mapping (integrated monopolar with suction probe/ultrasonic aspirator)? *n*=77	• Yes • No • No answer	4 (17.4) 15 (65.2) 4 (17.4)	8 (32.0) 13 (52.0) 4 (16.0)	11 (37.9) 11 (37.9) 7 (24.1)	0.1592
Is transcortical magnetic stimulation (TMS) used for asleep mapping? *n*=77	• Yes • No • No answer	0 20 (87.0) 3 (13.0)	2 (8.0) 19 (76.0) 4 (16.0)	3 (10.3) 19 (65.6) 7 (24.1)	0.6075

Table 7: Procedural preferences for asleep mapping specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
How are eloquent areas identified during asleep mapping? (select one or more answers) *n*=77	• SSEPs (somato-sensory evoked potentials)	14 (60.9)	18 (72.0)	18 (62.1)	0.8256
	• MEPs (motor evoked potentials)	21 (91.3)	20 (80.0)	20 (69.0)	
	• CMAPs (compound motor action potentials)	3 (13.0)	3 (12.0)	5 (17.2)	
	• ADPs (after-discharge potentials)	5 (21.7)	4 (16.0)	1 (3.4)	
	• Phase reversal	15 (65.2)	13 (52.0)	12 (41.4)	
	• Other	0	0	0	
Is a clinical neurophysiologist present and is telemetric monitoring used during asleep mapping? *n*=77	• Yes, with telemetric monitoring	11 (47.8)	9 (36.0)	10 (34.5)	0.5417
	• Yes, without telemetric monitoring	6 (26.1)	6 (24.0)	10 (34.5)	
	• Neurophysiologist is not present	5 (21.7)	9 (36.0)	5 (17.2)	
	• No answer	1 (4.3)	1 (4.0)	4 (13.8)	
Are surgical adjuncts or additional (intraoperative) imaging modalities used during asleep mapping? (select one or more answers) *n*=77	• Fluorescence/5-ALA	10 (43.5)	11 (44.0)	16 (55.2)	0.6872
	• Intraoperative MRI	2 (8.7)	5 (20.0)	10 (34.5)	
	• Intraoperative ultrasound	13 (56.5)	13 (52.0)	18 (62.1)	
	• Diffusion tensor imaging (DTI)	14 (60.9)	13 (52.0)	16 (55.2)	
	• Functional MRI (fMRI)	11 (47.8)	12 (48.0)	9 (31.0)	
	• None	2 (8.7)	1 (4.0)	0	
Are ECoG or intraoperative EEG used during asleep mapping? *n*=77	• ECoG only	5 (21.7)	4 (16.0)	4 (13.8)	0.1452
	• EEG only	1 (4.3)	2 (8.0)	4 (13.8)	
	• Both	1 (4.3)	5 (20.0)	8 (27.6)	
	• None	11 (47.8)	9 (36.0)	5 (17.2)	
	• No answer	5 (21.7)	5 (20.0)	8 (27.6)	

Table 8: Perioperative decision making specified by surgeon's experience

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
Part 4 – Decision making					
On which information is your decision to end the resection based? (1-10 for each answer, 1 meaning not important at all and 10 meaning extremely important) *n*=121	• The patient's task performance, which decreases significantly during awake craniotomy and suggests that maximum safe resection is reached	Median 10 [1-10]	Median 10 [1-10]	Median 10 [1-10]	NA
	• The evoked potentials, which show that the amplitude diminishes significantly and suggests that maximum safe resection is reached	Median 8 [1-10]	Median 9 [7-10]	Median 8 [1-10]	
	• The imaging, which suggests that maximum safe resection is reached (based on either the neuronavigation, DTI, fMRI or ioMRI)	Median 8 [1-10]	Median 8 [2-10]	Median 7.5 [1-10]	
	• The macroscopy, which indicates a gross-total resection (GTR) and suggests that a maximum macroscopic resection is reached (based on either your expertise or 5-ALA)	Median 8 [1-10]	Median 8 [1-10]	Median 8 [3-10]	
	• None of the above	0	0	2 (5.3)	
	• No answer	5 (11.6)	3 (6.7)	2 (5.3)	
How are initial stimulation-induced seizures suppressed? (select one or more answers) *n*=121	• Irrigating the exposed brain surface with chilled sodiumchloride solution	13 (30.2)	16 (35.6)	17 (44.7)	0.7089
	• Irrigating the exposed brain surface with chilled Ringer's lactate solution	5 (11.6)	15 (31.3)	11 (24.4)	
	• Administration of anti-epileptic medication	6 (14.0)	11 (22.9)	11 (24.4)	
	• Other	0	0	2 (5.3)	
	• None of the above	2 (4.7)	2 (4.2)	2 (5.3)	
	• No answer	18 (41.9)	9 (18.8)	4 (8.3)	

Table 8: Perioperative decision making specified by surgeon's experience

Question	Response options	<100 glioma resections performed (%)	100-500 glioma resections performed (%)	>500 glioma resections performed (%)	*P* value
How are recurrent stimulation-induced seizures treated? (select one or more answers) *n*=121	• Irrigating the exposed brain surface with chilled sodiumchloride solution	11 (25.6)	15 (31.3)	16 (35.6)	0.3677
	• Irrigating the exposed brain surface with chilled Ringer's lactate solution	5 (11.6)	12 (25.0)	11 (24.4)	
	• Administration of anti-epileptic medication	14 (32.6)	18 (37.5)	21 (46.7)	
	• Administration of intravenous propofol	5 (11.6)	19 (39.6)	13 (28.9)	
	• Administration of intravenous benzodiazepines	8 (18.6)	4 (8.3)	7 (15.6)	
	• The mapping procedure is replaced by asleep mapping and the resection is continued	4 (9.3)	7 (14.6)	3 (6.7)	
	• The mapping procedure is definitively terminated and the resection is continued under general anesthesia	2 (4.7)	6 (12.5)	5 (11.1)	
	• Other	1 (2.2)	0	1 (2.2)	
	• None of the above	2 (4.7)	2 (4.2)	3 (6.7)	
	• No answer	17 (39.5)	9 (18.8)	4 (8.3)	

CHAPTER 13

Decision making and surgical modality selection in glioblastoma patients: an international multicenter survey

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ABSTRACT

Purpose

Due to the lack of consensus on the management of glioblastoma patients, there exists variability amongst surgeons and centers regarding treatment decisions. Though, objective data about the extent of this heterogeneity is still lacking. We aim to evaluate and analyze the similarities and differences in neurosurgical practice patterns.

Methods

The survey was distributed to members of the neurosurgical societies of the Netherlands (NVVN), Europe (EANS), the United Kingdom (SBNS) and the United States (CNS) between January and March 2021 with questions about the selection of surgical modality and decision making in glioblastoma patients.

Results

Survey respondents (224 neurosurgeons) were from 41 countries. Overall, the most notable differences observed were the presence and timing of a multidisciplinary tumor board; the importance and role of various perioperative factors in the decision-making process, and the preferred treatment in various glioblastoma cases and case variants. Tumor boards were more common at academic centers. The intended extent of resection for glioblastoma resections in eloquent areas was limited more often in European neurosurgeons. We found a strong relationship between the surgeon's theoretical survey answers and their actual approach in presented patient cases. In general, the factors which were found to be theoretically the most important in surgical decision making were confirmed to influence the respondents' decisions to the greatest extent in practice as well.

Discussion

This survey illustrates the theoretical and practical heterogeneity among surgeons and centers in their decision making and treatment selection for glioblastoma patients. These data invite further evaluations to identify key variables that can be optimized and may therefore benefit from consensus.

INTRODUCTION

Guidelines for the management of neurosurgical disease have been published by national and international neurosurgical societies in partnership with other specialties. Despite these widely accepted guidelines, neurosurgeons practice patterns differ within an institution, and amongst centers nationally and internationally based upon a surgeon's individual expertise and preference. The neurosurgical management of brain tumors requires a balance of neurosurgical guidelines with patient specific characteristics and the surgeon's individual experience to determine the optimal treatment. Surgeons decide on whether to operate, the extent of resection (ranging from no surgery, biopsy, debulking, to maximal safe resection), the use of mapping techniques (e.g. awake craniotomy) [1,2], the use of surgical adjuncts (e.g. fluorescence) [3] and the use of additional imaging (e.g. fMRI, intraoperative MRI, intraoperative ultrasound, DTI) [4-9]. Factors that could influence the surgeon's decision range from the patient's age, comorbidities and preference, the preoperative functioning and morbidity of the patient, to the size, location and eloquence of the tumor [10-13]. The neurosurgical field is still divided on a number of these factors, examples of which are: how aggressive one should operate on GBM patients, the added value of mapping techniques in GBMs in or near eloquent areas, and if one should be restrained with performing a resection among elderly GBM patients (and should opt for biopsy instead for example) [14-21].

The heterogeneity in decision making and treatment selection between surgeons and centers that differ in experience, affiliation and region has yet to be assessed objectively and globally.

This survey aims to evaluate the various layers of onco-neurosurgical decision making in both a theoretical and practical setting with special attention for multidisciplinary tumor boards, the patient-related and tumor-related factors that play a role in the decision-making process, the factors that influence the defensiveness/aggressiveness of the surgeon's approach, and his or her approach in selected cases which represent various subgroups of GBM patients. This survey will give insight in the neurosurgical practices for the treatment of these patients on a global scale and the reasons behind the similarities and differences between surgeons and why they make the choices they make. The goal is to conduct a contemporary benchmark assessment that will serve as a first step in reaching practice consensus in GBM patients for certain variables.

METHODS

Survey design

The questionnaire was constructed by the ENCRAM Research Consortium [22]. Questions were aimed to evaluate the local decision making and surgical modality selection in glioblastoma cases, especially regarding absence/presence multidisciplinary boards and its timing, attitude towards glioblastoma surgery (e.g., distinction between relatively aggressive or defensive), factors influencing this attitude in specific cases (e.g., tumor location, patient age) and factors influencing the decision between biopsy and resection. A sizable part of the survey focused on evaluating the respondent's choice and rationale for a surgical modality in example cases of different subgroups of glioblastoma patients. The target audience included consultant neurosurgeons (attendings) and neurosurgery fellows in neuro-oncology. These providers were divided in 3 groups: neurosurgery consultants/attendings with >5 years as experience as a neurosurgeon after their residency, neurosurgery consultants/attendings with <5 years as experience as a neurosurgeon after their residency, and neurosurgery fellows. Additional baseline characteristics included country, gender, number of glioma resections performed and place of practice (academic, non-academic, private practice). Academic centers are institutes that include both a teaching hospital and medical school and provide mostly specialized tertiary care. Non-academic centers are community hospitals that provide mostly secondary care to the community. Private practices are institutes that are paid for and owned by investors rather than by governments (United Kingdom: medical care that is not part of the National Health Service, NHS).

Survey dispersal

The survey was made available by a link to the online LimeSurvey questionnaire platform (LimeSurvey GmbH, Hamburg, Germany) and were distributed twice by electronic mailing lists of the Congress of Neurological Surgeons (CNS) and the Dutch Neurosurgical Association (NVVN) with Mailchimp (Atlanta, GA, USA). It was included twice in the monthly newsletter of the European Association of Neurological Societies (EANS) and distributed among the members of the British Society of Neurological Surgeon (SBNS) by mail. Participation in the survey was voluntary and without remuneration. Response rate was 5.0% among CNS members, 2.7% among SBNS members and 16.0% among NVVN members. Response rate among EANS members could not be assessed due to the nature of the survey's dispersal. The survey was open for entries between January and March 2021.

Statistical analysis

Survey data were exported for further data analysis on March 6th, 2021 from LimeSurvey into an Excel file and analyzed using *R* version 4.0.3 (the *R* foundation, Vienna, Austria). Data were grouped according to the baseline characteristics gender, WHO region, type

of institute, surgeon training level and the number of glioma resections the surgeon had performed. Overall response differences were analyzed using the χ^2 test for proportions with the Marascuillo procedure and Bonferroni correction for multiple testing. For responses with an observed count of <10 and/or expected count of <5 the Fisher's exact test was used. Categorical survey responses were further analyzed for different subgroups using multivariate logistic (logit) regression with type of institute and region (Europe/US) as the two independent variables. Continuous survey outcomes were analyzed using multinominal linear regression. For variables with >2 response options, dummy coding was used for processing responses into dichotomous variables. For questions that allowed multiple answers, the McFadden MNL model was used as a mixed effects model to analyze subgroup responses. Univariate logistic regression was used to further analyze the case responses with reported factor importance and region (Europe/US) as the independent variables. Statistical significance was set at 5%.

RESULTS

We obtained a total of 224 responses from 41 countries. Table S1 (Data Supplement) shows the baseline characteristics of the respondents. 202 survey participants were male (90.2%) and 22 participants were female (9.8%).

Thirty-seven percent of the responses originated from the United States and Canada (*n*=83), 7.6% from Latin America (*n*=17), 40.6% from Europe (*n*=91), 3.1% from the Eastern Mediterranean Region (*n*=7), 4.5% from South-East Asia (*n*=10), 4.9% from the Western Pacific (*n*=11) and 2.2% from the African Region (*n*=5) (Table S1, Figure S1, Data Supplement). These countries included (absolute *n* of responses in parentheses): American Samoa (1), Argentina (4), Australia (3), Austria (2), Belgium (5), Brazil (2), Canada (6), Chile (1), China (1), Colombia (4), Czech Republic (1), Egypt (1), Finland (1), France (3), Germany (7), Greece (2), India (5), Indonesia (3), Iran (1), Ireland (1), Italy (5), Jordan (1), Mexico (4), Nepal (2), the Netherlands (24), Nigeria (1), Pakistan (1), Peru (2), Philippines (1), Portugal (3), Romania (3), Serbia (3), South Africa (4), South Korea (3), Spain (2), Sudan (3), Switzerland (1), Taiwan (1), Turkey (2), United Arab Emirates (1), United Kingdom (26) and the United States (77). 62.9% of participants was appointed at an academic practice/university hospital (*n*=141), 19.2% worked at a non-academic practice/community hospital (*n*=43), 14.3% was appointed at a private practice (*n*=32) and 4.2% selected "other" as their current appointment (*n*=8). The majority of survey respondents concerned consultant neurosurgeons with >5 years of practice after finishing their fellowship (82.6%, *n*=185), 13.4% still had less than 5 years of experience (*n*=30). 3.6% of respondents were currently appointed as neurosurgical fellow (*n*=8), and one respondent was still in her residency.

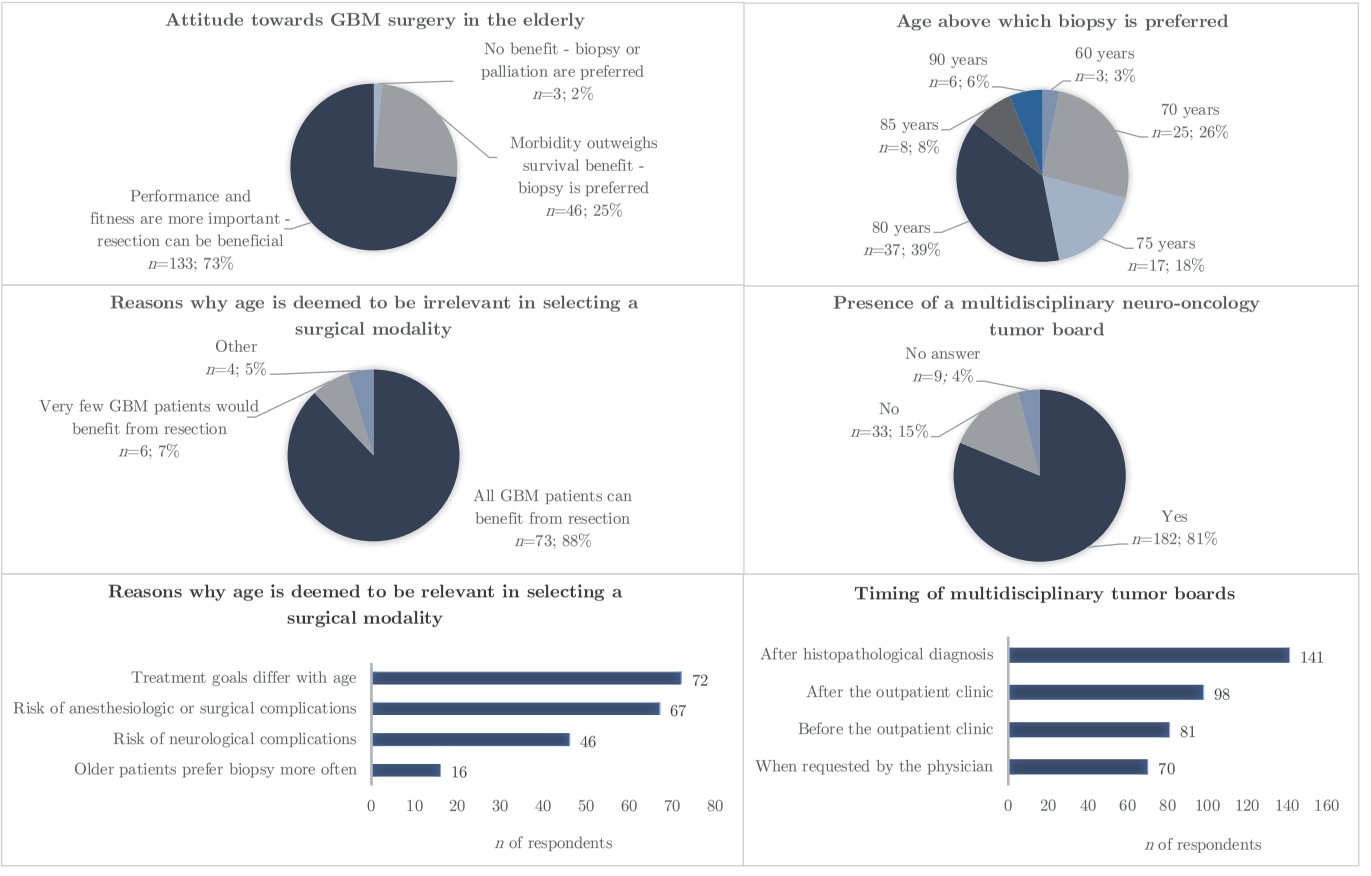


Figure 1: Significant differences – General decision making and attitude towards GBM surgery in the elderly

Experience with glioma surgery differed between respondents: 24.6% had performed less than 100 glioma resections (*n*=55), 51.3% had performed between 100 and 500 resections (*n*=115) and 24.1% had performed more than 500 resections (*n*=54).

General decision making

Overall responses were significantly different for 7 of the 8 questions (Table S2, Data Supplement). Multivariate subgroup analyses for academic vs. non-academic/private practice respondents and European vs. US neurosurgeons were significant for 3 of the 8 questions. Two hundred and twenty-four neurosurgeons reported on the decision making in GBM patients at their center. At a majority of centers, a multidisciplinary neuro-oncology tumor board was present (81.3%, p<0.0001, Figure 1), and significantly more often at academic centers (OR=8.05, p=0.0021). The most common timing of this board was after the definitive histopathological diagnosis (77.5%, p<0.0001). European respondents reported more often the presence of a tumor board prior to the outpatient clinic (OR=4.78, p<0.0001), while their US colleagues more often held a tumor board after the histopathological diagnosis (OR=0.28, p=0.0051). Respondents indicated on a Likert scale the extent to which various factors influence their decision when choosing a treatment modality for GBM patients (a rating of 1 meaning not important at all and 5 meaning very important). Tumor location and eloquence was rated the most important factor (mean 4.3), followed by preoperative patient functioning (mean 4.2), preoperative neurological morbidity (mean 4.0), patient's preference (mean 3.8), comorbidities (mean 3.6), patient's age (3.4), preoperative tumor size (mean 3.0) and the patient's social circumstances (mean 2.6) (Figure 2). Among the respondents who rated "age" an important or very important factor in their decision

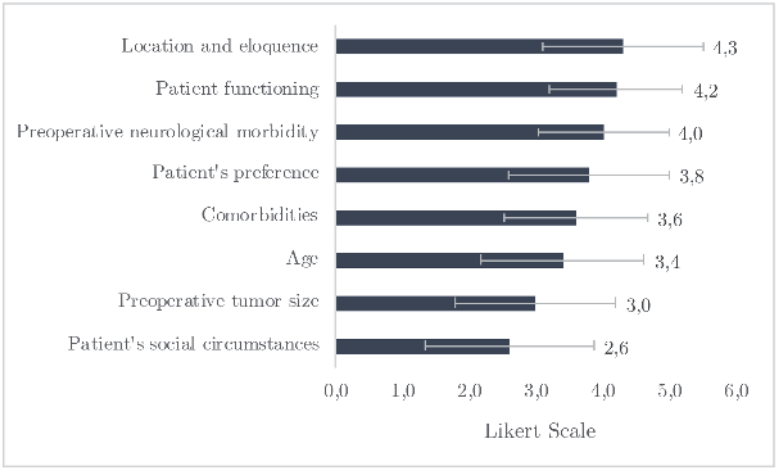


Figure 2: Impact of perioperative factors on surgical modality selection in GBM patients

making (Likert scale 4 or 5), the reason for this was most commonly that the treatment's goals differ for younger and older GBM patients (74.2%), followed by an increasing risk of anesthesiologic or surgical complications with increasing age (69.1%), increasing risk of neurological complications with increasing age (47.4%) and that older patients more often prefer a biopsy (16.5%). Moreover, the patient's age above which they would be more inclined to choose a biopsy rather than a resection was for the majority of respondents 80 years old (38.1%), (Figure 2). Overall, the majority of respondents agreed that the patient's age should be approached relatively since performance and fitness are ultimately more important, and that resection followed by adjuvant therapy is usually the best choice in GBM patients (71.5%), $p<0.0001$). However, almost a quarter of respondents (24.7%) reported that in their opinion, in older GBM patients the risk of morbidity outweighs the potential survival benefit and that biopsy followed by adjuvant therapy is usually the best choice for these patients. Moreover, respondents were asked to indicate whether various perioperative factors would, in their opinion, warrant a more aggressive (i.e. resection) or defensive (i.e. biopsy) approach which are illustrated in Figure 3. Survey responses for all questions were further analyzed to evaluate the impact of the surgeon's experience [in glioma surgery] on their answers (Table S3). The only significant difference was regarding attitude towards glioblastoma surgery in elderly patients: experienced neurosurgeons more often agreed with the statement that in older patients, the risk of morbidity outweighs survival benefit and that biopsy is often the best choice. Less experienced colleagues however found fitness and performance more important and were more inclined to perform a resection. For these perioperative factors, no significant differences were observed in the subgroup analyses for academic vs. non-academic/private practice surgeons. Though, US colleagues were slightly less defensive when tumors were located in or near eloquent areas (biopsy; OR=0.22; $p=0.0020$).

GBM patient cases

Respondents were asked to select their preferred treatment modality in four different GBM cases. Response options were: best supportive care, chemotherapy/radiotherapy only, biopsy, debulking, maximum resection without mapping, and maximum resection with mapping. Biopsy, debulking and maximum resection were followed by adjuvant therapy. If respondents selected debulking or maximum resection (with or without mapping) as their treatment of preference, they were asked to indicate whether they would use one or more surgical adjuncts or additional imaging. After completion of the original patient case, respondents were asked if their approach would change in various case variants (more aggressive, same approach, or more defensive), in which one or more perioperative factors were altered (while the rest of the case remained the same). More aggressive and more defensive indicate that the surgeon would choose a *treatment modality* which would be more aggressive ("up the ladder") or more defensive ("down the ladder"), respectively. Consequently,

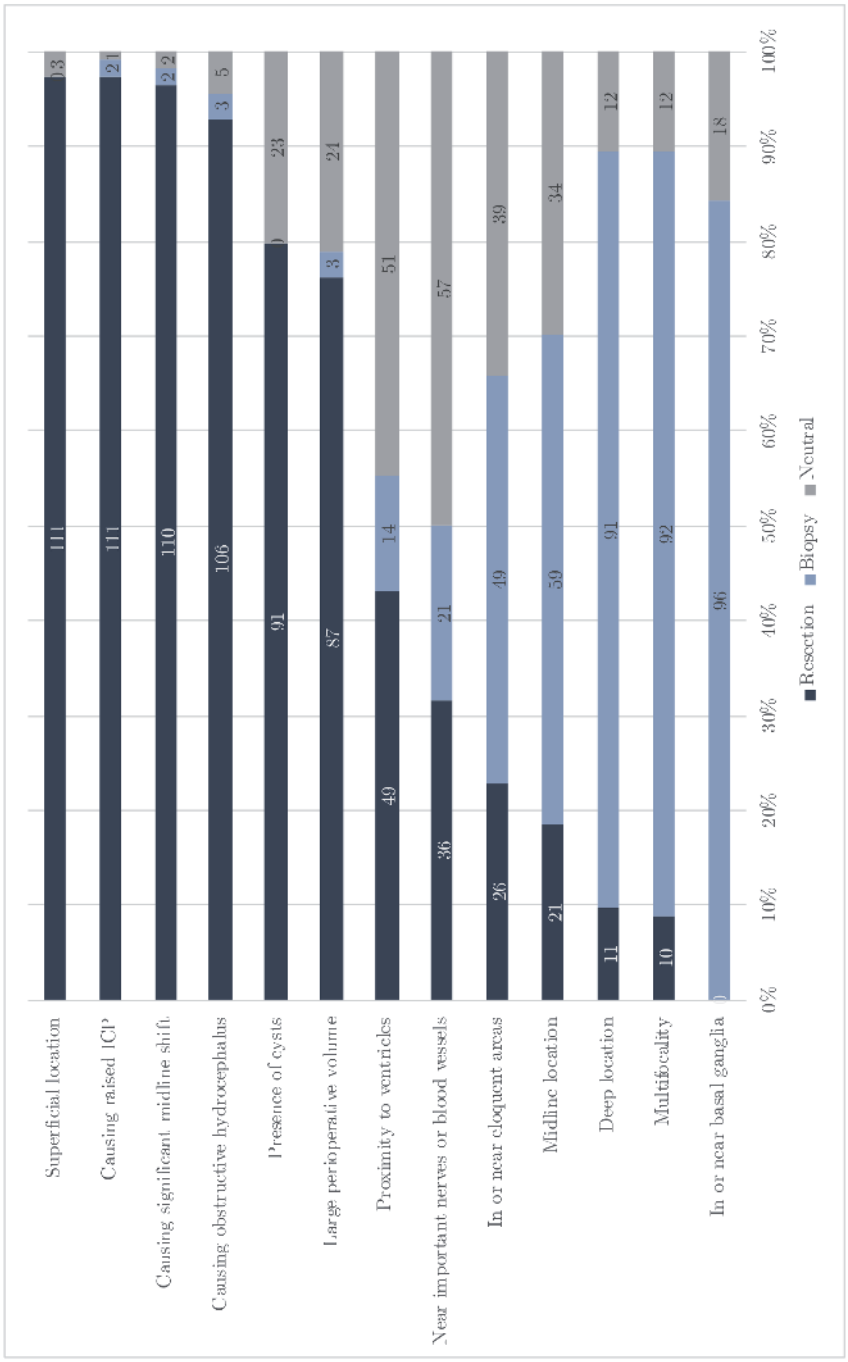


Figure 3: Impact of tumor related factors on surgical modality selection in GBM patients

respondents who preferred a maximum resection with mapping or best supportive care in the original case could not be more aggressive or more defensive in the case variants, respectively. Moreover, the results were further analyzed to evaluate respondents from which initial treatment group switched their approach when the case variant was presented. With regression analysis, an additional analysis was performed to investigate if this switch was in line with the respondent's earlier reported Likert scale rating for this particular factor, and if there were any differences between European and US surgeons. The results of these responses are summarized in Tables 1A-D, Table 2 and Figures 4A-D.

Case 1

The clinical details of case 1 are described in the text box of Figure 4A.

The majority of respondents preferred maximum resection with mapping (56.1%) significantly more often than maximum resection without mapping (38.7%, p=0.0022) and debulking (5.2%, p<0.0001) (Table 1A, Figure 4A). No respondents preferred a biopsy, chemotherapy or radiotherapy only or best supportive care.

In case variant 1 (elderly patient), a majority of respondents who preferred maximum resection with mapping and without mapping chose the same approach (with mapping: 73.4%, without mapping: 84.3%) (p<0.0001) (Table 1A). Though, a slight majority of respondents who preferred debulking chose to be more defensive (57.1%). Regression analysis showed that respondents who had reported the factor age as important or very important earlier in the survey were indeed more defensive in case variant 1 when the patient was older (OR=4.89, 95% CI 1.84-13.00, p=0.0015) (Table 1A).

In case variant 2 (ASA III, KPS 60), the majority of respondents who preferred maximum resection with mapping in the original case or debulking reported to be more defensive in this case variant (maximum resection with mapping: 59.2%, debulking: 57.1%), while respondents who preferred maximum resection without mapping chose the same approach more often (54.9%) (Table 1A). Overall, there was no significant difference between the same approach and a more defensive approach (p=0.2736). There was a nonsignificant relationship with earlier reported Likert scales on patient functioning (OR=2.43, 95% CI 0.90-6.54, p=0.0798) and comorbidities (OR=1.67, 95% CI 0.84-3.32, p=0.1465) (Table 1A).

In case variant 3 (right frontal tumor without hemiparesis), the majority of respondents who preferred maximum resection with mapping or without mapping indicated that they would choose the same approach (maximum resection with mapping: 96.1%, without mapping: 90.2%), whereas a slight majority of respondents who preferred debulking indicated they would be more aggressive in this case variant (42.9%) (Table 1A). Overall, most respondents

Case 1

Male, 36 y/o

Past medical history: blank

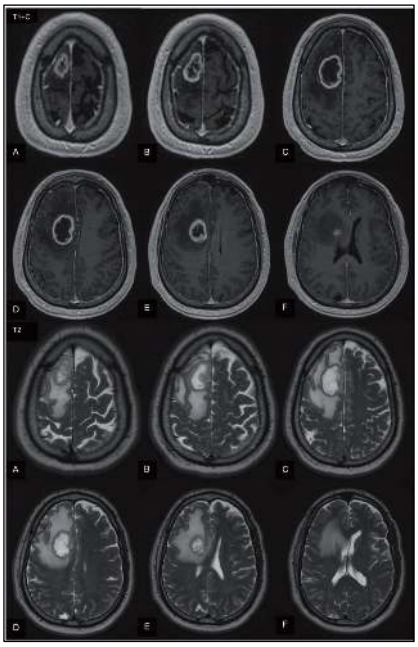
History and physical: decreased strength and coordination in the left upper extremity for 3 months. No headache, no nausea, no vomitus. Prefers an aggressive resection.

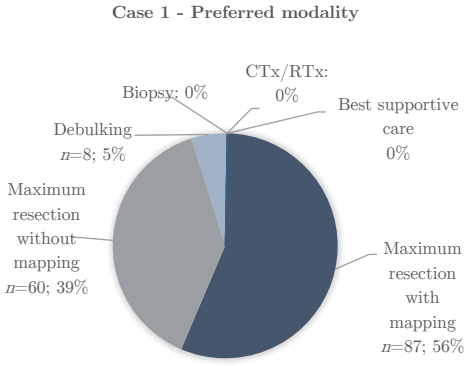
Neurological examination: Barré -/+, left-sided hemiparesis MRC grade 4. KPS: 100. MMSE: 30/30.
MRI + Gd: space-occupying lesion with contrast enhancement and extensive perifocal edema in the right frontoparietal region, suspected primary high-grade glioma

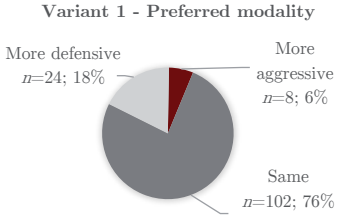
Which surgical treatment would you prefer in this case?

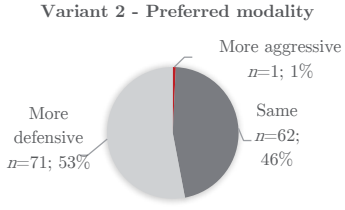
NB: for adjuncts, select one or more answers

Case variants: 1) older patient (75 years old); 2) ASA III, KPS 60; 3) right frontal tumor, no hemiparesis









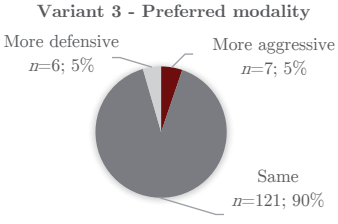


Figure 4A: Treatment modality selection in various GBM cases

Table 1A: Treatment modality selection in various GBM cases

Case	Response options	Response (%)	*P* value	Case variant 1 Pt 75 y/o		Case variant 2 ASA III, KPS 60		Case variant 2 Right frontal No hemiparesis	
Case 1 *n*=155 Male, 36 y/o Past medical history: blank History and physical: decreased strength and coordination in the left upper extremity for 3 months. No headache, no nausea, no vomitus. Prefers an aggressive resection. Neurological examination: Barré -/+, left-sided hemiparesis MRC grade 4. KPS: 100. MMSE: 30/30. MRI + Gd: space-occupying lesion with contrast enhancement and extensive perifocal edema in the right frontoparietal region, suspected primary high-grade glioma Which surgical treatment would you prefer in this case? NB: for adjuncts, select one or more answers	• Maximum resection with mapping	87 (56.1)[a]	$_{a/b}$ 0.0022*	Same	56 (73.4)	Same	31 (40.8)	Same	73 (96.1)
	o No adjuncts	3	$_{a/c}$<0.0001*	↓	20 (26.3)	↓	45 (59.2)	↓	3 (3.9)
	o Intraoperative ultrasound	15	$_{b/c}$<0.0001*						
	o Intraoperative MRI	9							
	o Functional MRI	15							
	o DTI	16							
	o Fluorescence	37							
	• Maximum resection without mapping	60 (38.7)[b]		↑	8 (15.7)	↑	1 (2.0)	↑	4 (7.8)
	o No adjuncts	14		Same	43 (84.3)	Same	28 (54.9)	Same	46 (90.2)
	o Intraoperative ultrasound	10		↓		↓	22 (43.1)	↓	1 (2.0)
	o Intraoperative MRI	4							
	o Functional MRI	9							
	o DTI	9							
	o Fluorescence	24							
	• Debulking followed by adjuvant therapy	8 (5.2)[c]		↑	0	↑	0	↑	3 (42.9)
	o No adjuncts	2		Same	3 (42.9)	Same	3 (42.9)	Same	2 (28.6)
	o Intraoperative ultrasound	3		↓	4 (57.1)	↓	4 (57.1)	↓	2 (28.6)
	o Intraoperative MRI	2							
	o Functional MRI	0							
	o DTI	0							
	o Fluorescence	1							
	• Biopsy followed by adjuvant therapy	0			NA		NA		NA
	• Chemotherapy or radiotherapy only	0			NA		NA		NA
	• Best supportive care	0			NA		NA		NA

chose the same approach as in the original case (p<0.0001). European and US neurosurgeons did not differ in treatment preferences for all three case variants.

Case 2

The clinical details of case 2 are described in the text box of Figure 4B.

The majority of respondents preferred maximum resection without mapping (71.7%) significantly more often than maximum resection with mapping (13.2%, p<0.0001) and debulking (11.2%, p<0.0001) (Table 1B, Figure 4B). Two respondents preferred a biopsy, 1 respondent preferred chemotherapy or radiotherapy only and two respondents preferred best supportive care.

In case variant 1 (younger patient), a majority of respondents who preferred maximum resection with mapping, without mapping or debulking chose the same approach (maximum resection with mapping: 100%, without mapping: 92.7%, debulking: 58.3%) (p<0.0001) (Table 1B). Regression analysis showed that respondents who had reported the factor "age" as important or very important earlier in the survey were indeed more aggressive in case variant 1 when the patient was younger (OR=7.53, 95% CI 1.63-34.70, p=0.0096) (Table 1B).

In case variant 2 (ASA III, KPS 60), the majority of respondents who preferred maximum resection with mapping in the original case chose the same approach (62.5%), as did respondents who originally preferred maximum resection without mapping (59.4%) (Table 1B). Overall, a majority of respondents chose the same approach for this case variant and the original case (p=0.0012). Regression analysis showed a significant relationship with earlier reported Likert scales on patient functioning (OR=4.52, 95% CI 1.28-15.98, p=0.0192) and comorbidities (OR=2.89, 95% CI 1.37-6.09, p=0.0054) (Table 2).

In case variant 3 (11 mm midline shift), the majority of respondents who preferred maximum resection with mapping, without mapping and debulking indicated that they would choose the same approach (maximum resection with mapping: 93.8%, without mapping: 92.7%, debulking: 66.7%) (Table 1B). Overall, most respondents chose the same approach as in the original case (p<0.0001). European and US neurosurgeons did not differ in treatment preferences for all three case variants.

Case 2

Female, 75 y/o

Past medical history: blank

History and physical: headache for 2 months, incidental finding on MRI.

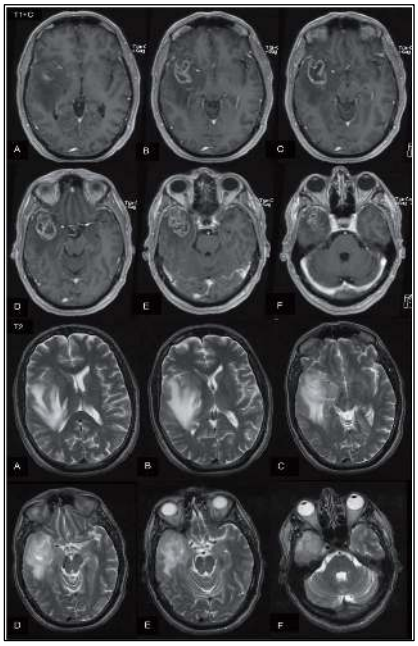
Neurological examination: normal. KPS: 100. MMSE: 30/30.

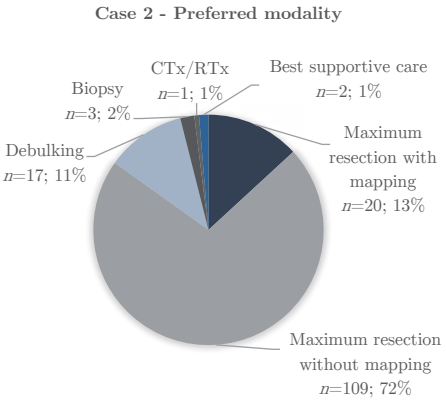
MRI + Gd: space-occupying lesion in the right temporal lobe. Irregular contrast enhancement, suspected for glioblastoma.

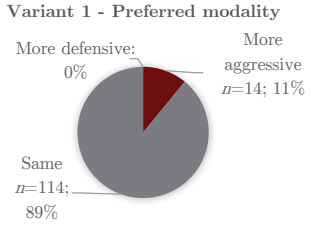
Which surgical treatment would you prefer in this case?

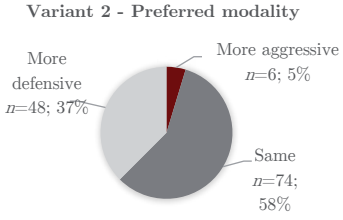
NB: for adjuncts, select one or more answers

Case variants: 1) younger patient (45 years old); 2) ASA III, KPS 60; 3) midline shift (11 mm)









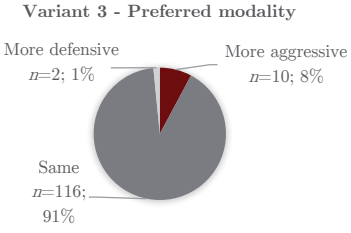


Figure 4B: Treatment modality selection in various GBM cases (continued)

Table 1B: Treatment modality selection in various GBM cases

Case	Response options	Response (%)	*P* value	Case variant 1 Patient 45 y/o		Case variant 2 ASA III, KPS 60		Case variant 3 11 mm MLS	
Case 2 *n*=152 Female, 75 y/o Past medical history: blank History and physical: headache for 2 months, incidental finding on MRI. Neurological examination: normal. KPS: 100. MMSE: 30/30. MRI + Gd: space-occupying lesion in the right temporal lobe. Irregular contrast enhancement, suspected for glioblastoma. Which surgical treatment would you prefer in this case? NB: for adjuncts, select one or more answers	• Maximum resection with mapping	20 (13.2)[b]	$_{a/b}$<0.0001*	Same	16 (100.0)	Same	10 (62.5)	Same	15 (93.8)
	o No adjuncts	2	$_{a/c}$<0.0001*	↓	0	↓	6 (37.5)	↓	1 (6.2)
	o Intraoperative ultrasound	3	$_{b/c}$<0.0001*						
	o Intraoperative MRI	4							
	o Functional MRI	3							
	o DTI	1							
	o Fluorescence	7							
	• Maximum resection without mapping	109 (71.7)[a]		↑	7 (7.3)	↑	0	↑	7 (7.3)
	o No adjuncts	29		Same	89 (92.7)	Same	57 (59.4)	Same	89 (92.7)
	o Intraoperative ultrasound	20		↓	0	↓	39 (40.6)	↓	0
	o Intraoperative MRI	10							
	o Functional MRI	8							
	o DTI	9							
	o Fluorescence	46							
	• Debulking followed by adjuvant therapy	17 (11.2)[b]		↑	5 (41.7)	↑	6 (50.0)	↑	3 (25.0)
	o No adjuncts	5		Same	7 (58.3)	Same	6 (50.0)	Same	8 (66.7)
	o Intraoperative ultrasound	4		↓	0	↓	0	↓	1 (8.3)
	o Intraoperative MRI	1							
	o Functional MRI	0							
	o DTI	1							
	o Fluorescence	6							
	• Biopsy followed by adjuvant therapy	3 (2.0)[c]		↑	1 (50.0)	↑	0	↑	0 (41.7)
				Same	1 (50.0)	Same	0	Same	2 (58.3)
				↓	0	↓	2 (100.0)	↓	0
	• Chemotherapy or radiotherapy only	1 (0.66)[c]		↑	1 (100.0)	↑	0	↑	0
				Same	0	Same	0	Same	1 (100.0)
				↓	0	↓	1 (100.0)	↓	0
	• Best supportive care	2 (1.3)[c]		↑	0	↑	0	↑	0
				Same	1 (100.0)	Same	1 (100.0)	Same	1 (100.0)

Case 3

The clinical details of case 3 are described in the text box of Figure 4C.

The majority of respondents preferred a biopsy (58.8%) significantly more often than debulking (26.1%, p<0.0001) and maximum resection (with mapping: 0.65, without mapping: 8.5%; p<0.0001) or chemotherapy/radiotherapy only (1.3%) or best supportive care (4.6%) (p<0.0001) (Table 1C, Figure 4C). European respondents were more likely to choose biopsy for this case than their US colleagues (OR=3.52, 95% CI 1.63-7.59, p=0.0014).

In case variant 1 (elderly patient), a majority of respondents who preferred maximum resection without mapping or biopsy chose the same approach (maximum resection without mapping: 53.8%, biopsy: 69.6), while 61.3% of the respondents who preferred debulking chose a more defensive approach (Table 1C). Overall, the majority of respondents prefers the same approach for the case variant as in the original case (p<0.0001). Regression analysis showed that respondents who had reported the factor age as important or very important earlier in the survey were indeed more defensive in case variant 1 when the patient was older (OR=2.22, 95% CI 1.05-4.68, p=0.0358) (Table 2).

In case variant 2 (ASA III, KPS 60), the majority of respondents who preferred biopsy in the original case chose the same approach in this case variant (75.9%), as did the respondents who preferred maximum resection without mapping (76.9%) or debulking (66.7%). Notably, a majority of respondents who preferred best supportive treatment in the original case now indicated to be more aggressive (71.4%) (Table 1C). Overall, a majority of respondents chose the same approach for this case variant and the original case (p<0.0001). Regression analysis showed no relationship with earlier reported Likert scales on patient functioning (OR=1.10, 95% CI 0.37-3.58, p=0.8764) and comorbidities (OR=0.79, 95% CI 0.34-1.85, p=0.5964) (Table 1C).

Case 3

Male, 44 y/o

Past medical history: hypertension, ICD placement in 2016 for persistent ventricular arrhythmias following acute myocardial infarctions in 2012 and 2016.

History and physical: worsening headache for 4 months and personality changes, sometimes disoriented and apathic according to partner. No vision problems.

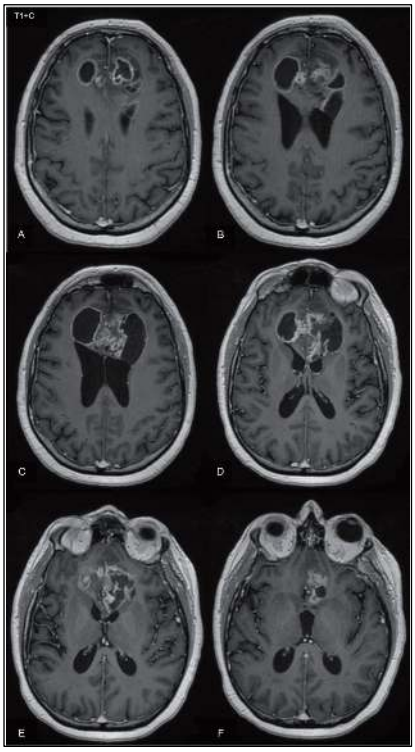
Neurological examination: normal. KPS: 70. MMSE: 21/30.

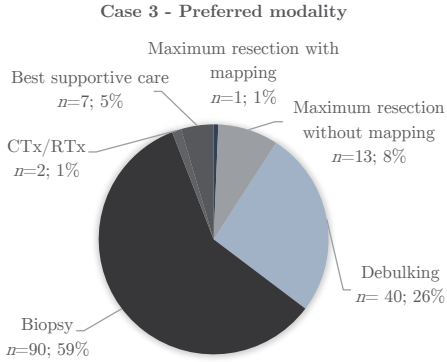
MRI + Gd: large multifocal contrast-enhancing lesion in both frontal lobes and corpus callosum. Inhomogeneous aspect with presence of both cysts and solid parts. Developing biventricular hydrocephalus.

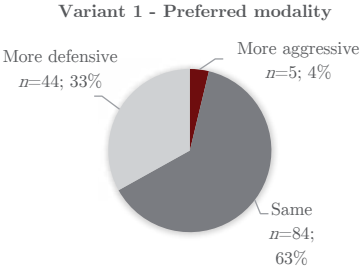
Which surgical treatment would you prefer in this case?

NB: for adjuncts, select one or more answers

Case variants: 1) older patient (75 years old); 2) ASA I, KPS 100, MMSE 30/30







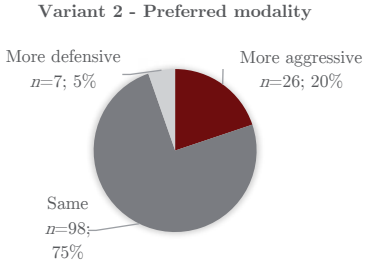


Figure 4C: Treatment modality selection in various GBM cases (continued)

Table 1C: Treatment modality selection in various GBM cases

Case	Response options	Response (%)	*P* value	Case variant 1 Patient 75 y/o		Case variant 2 ASA I, KPS 100, MMSE 30/30	
Case 3 *n*=153 Male, 44 y/o Past medical history: hypertension, ICD placement in 2016 for persistent ventricular arrhythmias following acute myocardial infarctions in 2012 and 2016. History and physical: worsening headache for 4 months and personality changes, sometimes disoriented and apathic according to partner. No vision problems. Neurological examination: normal. KPS: 70. MMSE: 21/30. MRI + Gd: large multifocal contrast-enhancing lesion in both frontal lobes and corpus callosum. Inhomogeneous aspect with presence of both cysts and solid parts. Developing biventricular hydrocephalus. Which surgical treatment would you prefer in this case? NB: for adjuncts, select one or more answers	• Maximum resection with mapping	1 (0.65)[c]	$_{a/b}$<0.0001*	Same	1 (100.0)	Same	1 (100.0)
	o No adjuncts	0	$_{a/c}$<0.0001*	↓	0	↓	0
	o Intraoperative ultrasound	0	$_{b/c}$<0.0001*				
	o Intraoperative MRI	0					
	o Functional MRI	0					
	o DTI	0					
	o Fluorescence	1					
	• Maximum resection without mapping	13 (8.5)[c]		↑	1 (7.7)	↑	1 (7.7)
	o No adjuncts	3		Same	7 (53.8)	Same	10 (76.9)
	o Intraoperative ultrasound	2		↓	5 (38.5)	↓	2 (15.4)
	o Intraoperative MRI	4					
	o Functional MRI	3					
	o DTI	2					
	o Fluorescence	6					
	• Debulking followed by adjuvant therapy	40 (26.1)[b]		↑	0	↑	4 (11.1)
	o No adjuncts	11		Same	12 (38.7)	Same	24 (66.7)
	o Intraoperative ultrasound	12		↓	19 (61.3)	↓	2 (5.6)
	o Intraoperative MRI	2					
	o Functional MRI	2					
	o DTI	4					
	o Fluorescence	11					
	• Biopsy followed by adjuvant therapy	90 (58.8)[a]		↑	0	↑	16 (20.3)
				Same	55 (69.6)	Same	60 (75.9)
				↓	24 (30.4)	↓	3 (3.8)
	• Chemotherapy or radiotherapy only	2 (1.3)[c]		↑	0	↑	0
				Same	1 (100.0)	Same	1 (100.0)
				↓	0	↓	0
	• Best supportive care	7 (4.6)[c]		↑	0	↑	5 (71.4)
				Same	7 (100.0)	Same	2 (28.6)

Case 4

The clinical details of case 4 are described in the text box of Figure 4D.

The majority of respondents preferred debulking (36.8%) significantly more often than maximum resection without mapping (20.4%) or best supportive care (17.1%) (p=0.0005), and also significantly more often than maximum resection with mapping (11.8%) or biopsy (16.4%) (p<0.0001). (Table 1D, Figure 4D). European respondents were more defensive and were more likely to prefer best supportive care (OR=9.24, 95% CI 3.00-28.47, p=0.0001), while US respondents were more aggressive and more often chose maximum resection without mapping (OR=0.28, 95% CI 0.11-0.69, p=0.0060).

In case variant 1 (younger patient), a majority of respondents who preferred maximum resection with or without mapping chose the same approach (maximum resection with mapping: 100%, without mapping: 82.1%). In contrast, a majority who originally preferred debulking, biopsy or best supportive care chose to be more aggressive in this situation (debulking: 63.4%, biopsy: 68.4%, best supportive care: 57.7%) (Table 1D). Overall, there was no significant difference between a more aggressive approach (46.1%) or the same approach (53.9%) for this case variant (p=0.2129). Regression analysis showed a nonsignificant relationship with earlier reported Likert scales on age (OR=1.74, 95% CI 0.85-3.56, p=0.1306) (Table 2).

In case variant 2 (right temporal tumor, no aphasia), the majority of respondents who preferred maximum resection with or without mapping in the original case chose the same approach in this case variant (maximum resection with mapping: 100%, without mapping: 78.6%). Similar to variant 1, the respondents who preferred debulking or biopsy in the original case reported more often to be more aggressive in this situation (debulking: 75.6%, biopsy: 68.4%), as did the respondents who preferred best supportive care earlier (84.6%) (Table 1D). Overall, a majority of respondents chose to be more aggressive in this case variant (p=0.0337). Regression analysis showed a significant relationship with earlier reported Likert scales on patient functioning (OR=4.52, 95% CI 1.28-15.98, p=0.0192) and comorbidities (OR=2.89, 95% CI 1.37-6.09, p=0.0054) (Table 2).

In case variant 3 (11 mm midline shift), similar to variants 1 and 2, the majority of respondents who were already aggressive in the original case choose the same approach in this situation (maximum resection with mapping: 100%, without mapping: 78.6%). The majority of respondents who were slightly more defensive in the original case choose to be more aggressive in this case variant (debulking: 56.1%, biopsy: 68.4%, best supportive care: 92.3%) (Table 1D). Overall, there was no significant difference between a more aggressive approach (51.6%) or the same approach (48.4%) for this case variant (p=0.6094). Regression analysis

Case 4

Female, 76 y/o

Past medical history: hypertension, bilateral peripheral arterial occlusive disease Fontaine III since 2010, cataract

History and physical: significant concentration problems and receptive aphasia. Morning sickness and frequent vomiting since last week. Two epileptic seizures last 3 days, treated with intranasal midazolam.

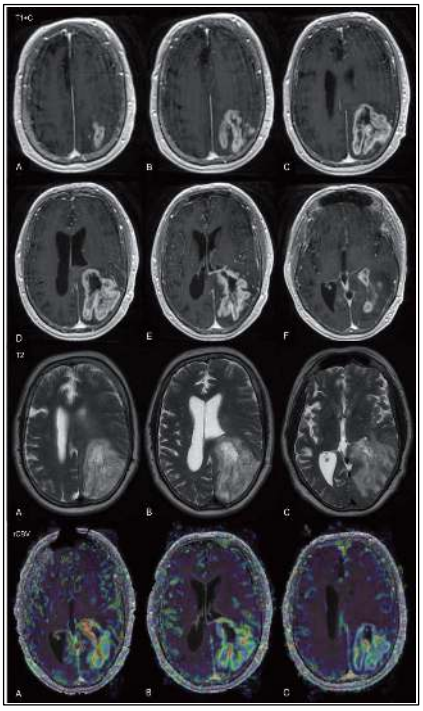
Neurological examination: E3V4M6, severe receptive aphasia, right-sided hemi-neglect, gait imbalance. KPS: 60.

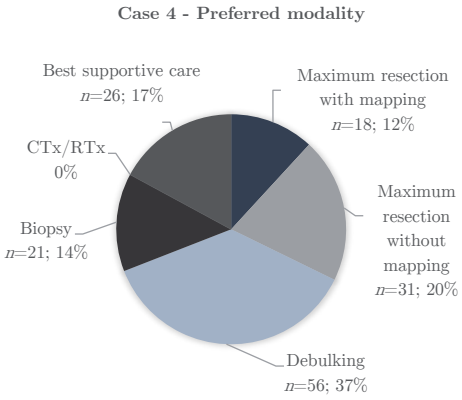
MRI + Gd: contrast-enhancing lesion in the left parieto-temporal lobe with extensive edema, possibly near Wernicke's area. Suspected GBM.

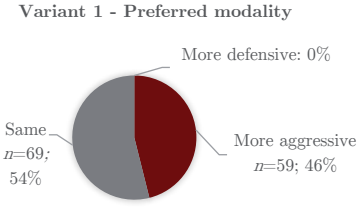
Which surgical treatment would you prefer in this case?

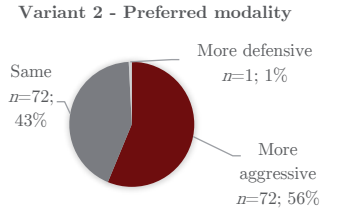
NB: for adjuncts, select one or more answers

Case variants: 1) younger (45 years old); 2) right temporal tumor, no aphasia; 3) GCS 15, ASA I, KPS 60









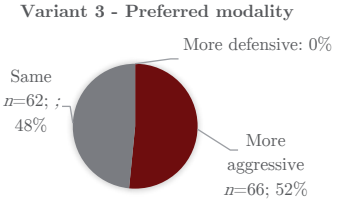


Figure 4D: Treatment modality selection in various GBM cases (continued)

Table 1D: Treatment modality selection in various GBM cases

Case	Response options	Response (%)	*P* value	Case variant 1 Patient 45/yo		Case variant 2 Right temporal No aphasia		Case variant 3 GCS 15, ASA I, KPS 100	
Case 4 *n*=152 Female, 76 y/o Past medical history: hypertension, bilateral peripheral arterial occlusive disease (PAOD) Fontaine III since 2010, cataract History and physical: significant concentration problems and receptive aphasia. Morning sickness and frequent vomiting since last week. Two epileptic seizures last 3 days, treated with intranasal midazolam. Neurological examination: E3V4M6 with severe receptive aphasia, right-sided hemi-neglect and gait imbalance. KPS: 60. MRI + Gd: contrast-enhancing lesion in the left parieto-temporal lobe with extensive edema, possibly near Wernicke's area. Suspected GBM. Which surgical treatment would you prefer in this case? NB: for adjuncts, select one or more answers	• Maximum resection with mapping	18 (11.8)[c]	$_{a/b}$ 0.0005* $_{a/c}$<0.0001* $_{b/c}$ 0.1472	Same	14 (100.0	Same	14 (100.0)	Same	14 (100.0)
	o No adjuncts	2		↓	0	↓	0	↓	0
	o Intraoperative ultrasound	3							
	o Intraoperative MRI	1							
	o Functional MRI	3							
	o DTI	3							
	o Fluorescence	9							
	• Maximum resection without mapping	31 (20.4)[b]		↑	5 (17.9)	↑	6 (21.4)	↑	6 (21.4)
	o No adjuncts	8		Same	23 (82.1)	Same	22 (78.6)	Same	22 (78.6)
	o Intraoperative ultrasound	8		↓	0	↓	0	↓	0
	o Intraoperative MRI	6							
	o Functional MRI	4							
	o DTI	4							
	o Fluorescence	11							
	• Debulking followed by adjuvant therapy	56 (36.8)[a]		↑	26 (63.4)	↑	31 (75.6)	↑	23 (56.1)
	o No adjuncts	17		Same	15 (36.6)	Same	10 (24.4)	Same	18 (43.9)
	o Intraoperative ultrasound	8		↓	0	↓	0	↓	0
	o Intraoperative MRI	6							
	o Functional MRI	4							
	o DTI	5							
	o Fluorescence	16							
	• Biopsy followed by adjuvant therapy	21 (13.8)[c]		↑	13 (68.4)	↑	13 (68.4)	↑	13 (68.4)
				Same	6 (31.6)	Same	5 (26.3)	Same	6 (26.4)
				↓	0	↓	1 (5.3)	↓	0
	• Chemotherapy or radiotherapy only	0			NA		NA		NA
	• Best supportive care	26 (17.1)[b]		↑	15 (57.7)	↑	22 (84.6)	↑	24 (92.3)
				Same	11 (42.3)	Same	4 (15.4)	Same	2 (7.7)

Table 2: Treatment modality selection in various GBM cases – Regression analyses

Case variant	Approach	Response (%)	*P* value	Adjusted OR for neurosurgeons who rated this factor important (4-5 Likert Scale) vs. neutral or unimportant (1-2-3) (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* Value
Case 1 Base	Max Rx, mapping +	87 (56.1)[a]	$_{a/b}$ 0.0022*	NA		0.80 (0.39-1.66)	0.5572
	Max Rx, mapping –	60 (38.7)[b]	$_{a/c}$<0.0001*			0.28 (0.051-1.49)	0.1340
	Debulking	8 (5.2)[c]	$_{b/c}$<0.0001*			0.59 (0.28-1.26)	0.1747
Case 1 Variant 1	More aggressive	8 (6.0)	$_{a/b}$<0.0001*			NA	
Older patient (75 years old)	Same	102 (76.1)[b]				0.64 (0.24-1.69)	"
Factor: Age	More defensive	24 (17.9)[a]		4.89 (1.84-13.00)	0.0015*	1.56 (0.59-4.09)	0.3707
Case 1 Variant 2	More aggressive	1 (0.75)	$_{a/b}$ 0.2736			NA	
ASA III, KPS 60	Same	62 (46.3)[b]				0.53 (0.24-1.14)	"
Factor: Preoperative functioning[†]	More defensive	71 (53.0)[a]		2.43 (0.90-6.54)[†]	0.0798	1.90 (0.88-4.12)	0.1021
Factor: Comorbidities[††]				1.67 (0.84-3.32)[††]	0.1465		
Case 1 Variant 3	More aggressive	7 (5.2)[a]	$_{a/b}$<0.0001*	NA		NA	
Right frontal, no hemiparesis	Same	121 (90.3)[b]					
Factor: Location and eloquence	More defensive	6 (4.5)					
Factor: Preoperative morbidity							
Case 2 Base	Max Rx, mapping +	20 (13.2)[b]	$_{a/b}$<0.0001*	NA		0.84 (0.24-2.93)	0.7894
	Max Rx, mapping –	109 (71.70[a]	$_{a/c}$<0.0001*			0.81 (0.35-1.92)	0.6397
	Debulking	17 (11.2)[b]	$_{b/c}$<0.0001*			1.70 (0.49-5.85)	0.4027
	Biopsy	3 (2.0)[c]				NA	
	CTx/RTx	1 (0.66)[c]				NA	
	Best supportive care	2 (1.3)[c]				NA	
Case 2 Variant 1	More aggressive	14 (10.9)[a]	$_{a/b}$<0.0001*			0.98 (0.30-3.13)	0.9677
Younger patient (45 years old)	Same	114 (89.1)[b]				1.02 (0.32-3.29)	"
Factor: Age	More defensive	0		7.53 (1.63-34.70)	0.0096*		

Table 2: Treatment modality selection in various GBM cases – Regression analyses (continued)

Case variant	Approach	Response (%)	*P* value	Adjusted OR for neurosurgeons who rated this factor important (4-5 Likert Scale) vs. neutral or unimportant (1-2-3) (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* Value
Case 2 Variant 2	More aggressive	6 (4.9)	$_{a/b}$ 0.0012*			NA	
ASA III, KPS 60	Same	74 (57.8)[b]				0.47 (0.21-1.05)	"
Factor: Preoperative functioning†	More defensive	48 (37.5)[a]		4.52 (1.28-15.98)†	0.0192*	2.13 (0.95-4.78)	0.0656
Factor: Comorbidities††				2.89 (1.37-6.09)††	0.0054*		
Case 2 Variant 3	More aggressive	10 (7.8)[a]	$_{a/b}$<0.0001*	NA		0.61 (0.13-2.87)	0.5299
Midline shift (11 mm)	Same	116 (90.6)[b]				1.64 (0.35-7.74)	"
Factor: None	More defensive	2 (1.6)					
Case 3 Base	Max Rx, mapping +	1 (0.65)[c]	$_{a/b}$<0.0001*	NA		NA	
	Max Rx, mapping –	13 (8.5)[c]	$_{a/c}$<0.0001*			NA	
	Debulking	40 (26.1)[b]	$_{b/c}$<0.0001*			0.50 (0.22-1.14)	0.0999
	Biopsy	90 (38.8)[a]				3.52 (1.63-7.59)	0.0014*
	CTx/RTx	2 (1.3)[c]				NA	
	Best supportive care	7 (4.6)[c]				NA	
Case 3 Variant 1	More aggressive	5 (3.8)	$_{a/b}$<0.0001*				
Older patient (75 years old)	Same	84 (63.2)[b]				1.12 (0.51-2.48)	"
Factor: Age	More defensive	44 (33.1)[a]		2.22 (1.05-4.68)	0.0358*	0.89 (0.40-1.97)	0.7743
Case 3 Variant 2							
ASA I, KPS 100,	More aggressive	26 (19.8)[a]	$_{a/b}$<0.0001*			1.19 (0.46-3.09)	0.7162
MMSE 30/30	Same	98 (74.8)[b]				0.84 (0.32-2.17)	"
Factor: Preoperative functioning†	More defensive	7 (5.3)		1.10 (0.37-3.58)†	0.8764		
Factor: Comorbidities††				0.79 (0.34-1.85)††	0.5946		

Table 2: Treatment modality selection in various GBM cases – Regression analyses (continued)

Case variant	Approach	Response (%)	*P* value	Adjusted OR for neurosurgeons who rated this factor important (4-5 Likert Scale) vs. neutral or unimportant (1-2-3) (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* Value
Case 4 Base	Max Rx, mapping +	18 (14.1)[b]	a/b 0.0003*	NA		0.56 (0.20-1.59)	0.2783
	Max Rx, mapping –	31 (24.2)[b]	a/c<0.0001*			0.28 (0.11-0.69)	0.0060*
	Debulking	56 (43.8)[a]	b/c 0.1472			1.14 (0.59-2.20)	0.7051
	Biopsy	21 (16.4)[c]				0.81 (0.32-2.02)	0.6481
	CTx/RTx	0				9.24 (3.00-28.47)	0.0001*
	Best supportive care	26 (20.3)[b]					
Case 4 Variant 1	More aggressive	59 (46.1)[a]	a/b 0.2129			2.31 (1.02-5.20)	0.0436*
Younger patient (45 years old)	Same	69 (53.9)[b]				0.43 (0.19-0.98)	"
Factor: Age	More defensive	0		1.74 (0.85-3.56)	0.1306		
Case 4 Variant 2							
Right temporal, no aphasia	More aggressive	72 (56.3)[a]	a/b 0.0337*			1.72 (0.77-3.83)	0.1833
Factor: Location and eloquence†	Same	55 (43.0)[b]		1.72 (0.66-4.51)†	0.2680	0.58 (0.26-1.29)	"
Factor: Preoperative morbidity††	More defensive	1 (0.078)		0.90 (0.37-2.23)††	0.8276		
Case 4 Variant 3							
GCS 15, ASA I, KPS 100	More aggressive	66 (51.6)[a]	a/b 0.6094			2.96 (1.31-6.69)	0.0088*
Factor: Preoperative functioning†	Same	62 (48.4)[b]		1.08 (0.40-2.91)†	0.8862	0.34 (0.15-0.76)	"
Factor: Comorbidities††	More defensive	0		1.54 (0.76-3.11)††	0.2310		

Legend: Max Rx = maximum resection. Mapping + = with mapping. Mapping - = without mapping. CTx = chemotherapy. RTx = radiotherapy. GCS = Glasgow Coma Scale. ASA = American Society of Anesthesiologists score. KPS = Karnofksy Performance Score. MMSE = Mini Mental State Examination. NB: the modalities biopsy, debulking, maximum resection without mapping and maximum resection with mapping include adjuvant chemoradiotherapy.

showed a very slight nonsignificant relationship with the earlier reported Likert scores on preoperative functioning (OR=1.08, 95% CI 0.40-2.91, p=0.8862) and comorbidities (OR=1.54, 95% CI 0.76-3.11, p=0.2310). Furthermore, European respondents were more likely to choose a more aggressive approach for variant 3 (OR=2.96, 95% CI 1.31-6.69, p=0.0088) (Table 2).

DISCUSSION

Key results

This survey is the first to investigate the local neurosurgical practices regarding treatment modality selection and decision making in GBM patients on a global scale. These practice variations were evaluated both on a theoretical and practical level (using patient cases) and further analyzed using multiple regression analyses for region, affiliation, and various perioperative factors' Likert scores.

We found a significant heterogeneity among surgeons and centers regarding their local decision-making practices as well as their surgical–treatment preferences glioblastoma patients. For the majority of the survey questions, the responses were significantly different between respondents. Overall, the most notable differences were observed for questions about the presence of a multidisciplinary neuro-oncology tumor board, the timing of this board, the importance of various perioperative factors in the decision-making process, the role and meaning of various perioperative factors in this process (aggressive vs. defensive approach), the reasons why the patient's age does or does not play a role in this process, how aggressive the treatment for GBM patients in general should be, the respondent's preferred treatment in various GBM cases, and the respondent's adaptation to multiple case variants. Subgroup analyses for affiliation using multivariate regression showed that multidisciplinary boards are more common at academic centers, whereas the analysis for region indicated that European neurosurgeons more commonly discuss the patient at these boards prior to the outpatient clinic. On the other hand, their US colleagues more commonly discuss the patient at these boards after the histopathological diagnosis. We do not have a clear explanation for this finding, although the highly centralized organization of hospitals and healthcare in Europe might play a role which may deem pre-clinic assessment and discussion of cases necessary.

Multivariate regression further showed that in some cases, US colleagues are slightly more aggressive in their surgical attitude: they are less likely to perform a biopsy when the tumor is located in or near eloquent areas, and more likely to have a more aggressive approach in patient cases 3 and 4. Moreover, the surgeon's reported importance of various perioperative

factors does often correspond with their case responses: in the case variants, respondents who had earlier in the survey rated the factor or factors that were altered important in their decision were more likely to change their approach.

Interpretation and comparison with the literature

We observed various significant differences between surgeons and centers in a theoretical and practical setting.

First, the difference in aggressiveness/defensiveness of European vs. US neurosurgeons which we observed in our results. The theoretical part of the survey showed that European neurosurgeons were almost five times less likely to have a neutral attitude towards the factor 'tumor located in or near eloquent areas' and were more than two times more likely to choose a biopsy in these cases. Their US colleagues however were more often neutral about this factor or preferred a resection (which could be both STR or GTR). To the best of our knowledge, the difference in attitude between EU and US neurosurgeons has not been reported in the previous literature. We would like to underline that our survey only studied the surgeon's preoperative attitude, which may not always reflect the intraoperative attitude (or surgical result) adequately. Surgeons who aim for GTR not always reach this goal and sometimes decide intraoperatively to go for STR instead. Furthermore, note that the observed differences in aggressiveness of attitude do not have any relationship with differences in skill level.

When evaluating the practical part of the survey, two cases included patients with an eloquent tumor (case 1: right frontoparietal causing hemiparesis; case 4: left parietotemporal causing aphasia). When analyzing these case responses, there is no significant difference in case 1 between European and US neurosurgeons, but for case 4 there is: US neurosurgeons were almost four times as likely to select 'maximum resection without mapping' as their preferred option, whereas European neurosurgeons were more than nine times more likely to select 'best supportive treatment' as their preferred choice. The fact that there is only a significant difference between EU/US neurosurgeons in case 4 and not in case 1 is of particular interest. One possible cause may be the fact that in case 1 almost 95% of respondents chose an aggressive approach (maximum resection with or without mapping). This in turn might be explained by the fact that the patient was in much better condition in case 1 than in case 4 (medical history, KPS, GCS, neurological examination), for which the responses were relatively evenly distributed between a very defensive approach (best supportive treatment) and a very aggressive one (maximum resection). The combined results on these cases might indicate that in young patients in good condition with eloquently located tumors, both European and US neurosurgeons opt for an aggressive approach. However, when a patient is older, has a suboptimal condition or has a significant amount of neurological morbidity,

European colleagues on average become more defensive, while their US colleagues still prefer an aggressive approach (on average, according to the practical part of our survey). Our data did provide us with a possible reason of this observation. Although we did not observe a difference in the theoretical importance of the factor "age" between European vs US neurosurgeons, the difference of the factor "Patient functioning (KPS)" was significant. Europeans were more inclined to deem this factor more important in their decision making. This might explain why they would have a slightly more defensive attitude in older patients with a suboptimal KPS. However, since the differences between European and US colleagues are relatively small these findings need to be validated in a second dataset.

Moreover, we further analyzed the data to evaluate if the factors that influence the surgeon's decision-making are the same in theory and practice. As mentioned above, case 1 described a relatively young and fit patient. Altering the patient's age or the location of the tumor does not significantly change the responses. However, when altering the ASA score (I to III) and KPS (100 to 60), a majority of respondents chooses a more defensive approach. This indicates that in fit patients, even when the tumor is located in or near eloquent areas, an overwhelming majority of surgeons still prefer to be relatively aggressive and that the preoperative functioning of the patient is for them more important than ~~both~~ either the patient's age or the tumor's location. This is partly in line with the reported Likert scores, in which the factor "location and eloquence" was rated with a mean of 4.3, "patient functioning" with a mean of 4.2 and "age" with a mean of 3.4. It is worth mentioning that even though the tumor in this case is eloquently located, almost 40% of respondents strive~~s~~ for maximum resection *without* mapping, which underlines the fact that mapping techniques are still not standard of care for these patients in all centers. The responses of case 2 are in line with case 1: age seems to be of lesser relevance ~~to~~ than patient functioning. In case 3, the patient is young but has a much worse overall functioning and neurological performance with the scan showing a classic butterfly glioma. Almost three-quarters of the respondents now choose to be more defensive and opt for debulking or biopsy instead. Increasing the patient's age to 75 makes the respondents' preferred approaches more defensive, more so in those who first preferred debulking. Improving the patient's fitness to ASA I/KPS 100/MMSE 30/30 makes their approaches slightly more aggressive (almost 20%), more so ~~in~~ from those who first preferred biopsy. Note that the increase in defensive approaches in the case of an older patient was larger than the increase in aggressive approaches in the case of a fitter patient. In this case, the location of the tumor (butterfly glioma) shows the decisive factor. In case 4, the patient is of older age, has an extensive past medical history, significant neurological morbidity (severe receptive aphasia) and suboptimal functioning and GCS (E3M6V4, KPS 60). Approximately a third of all respondents preferred an aggressive approach (maximum resection), a third chose to be more defensive (biopsy, best supportive care), and a third was in between (debulking). Lowering the patient's age, changing the tumor's location to

the right temporal lobe without causing aphasia or improving the patient's performance all led ~~to~~ almost half of the respondents to choose a more aggressive approach. All factors were relatively similar in their capacity to change the respondent's preferred treatment: tumor location and eloquence did so to the greatest extent followed by preoperative functioning and age (which is in accordance with the reported mean Likert scores). Thus, the factors which were found to be the most important in theory were confirmed to influence the respondents' decisions to the greatest extent in practice as well.

While guidelines exist on the management of neurosurgical disease, neurosurgical practices and treatment selection in brain tumor patients vary significantly depending on a surgeon's preferred approach, which results in varied behaviors (biopsy and resection). Recently, Müller *et al* published their results on a novel method to compare surgical decisions between two Dutch academic hospitals in GBM patients using probability brain maps [23]. In those two similar_cohorts, biopsy percentage differed significantly (21% vs. 40%, p=0.002). The location and volume of the tumor, nor the patient's age and_condition could ~~not~~ explain this difference. Moreover, there was significant_variation in the extent of tumor removal: one team more often resected tumor in the right caudate nucleus and anterior limb of the right internal capsule than the other team. They conclude that these differences may be related to a difference in risk/benefit decision making. Though, it remains unclear on which objective basis this would be.

Limitations and strengths

A notable limitation of a survey-based study such as this is sampling bias, while 224 neurosurgeons from 41 countries were surveyed, there are surgeons and centers that were not included in the study. In particular, the respondents skewed towards western countries from high-income countries. In addition, surgical decision making may reflect a center's culture on the surgeon's responses. Second, we did not have the depth of data to analyze the potential influence of the center's culture on the surgeon's responses. Third, our data did not allow for an additional analysis of the type of mapping (e.g awake vs. asleep, subcortical vs. cortical). Important strengths of this study include the survey's global distribution, the survey's combination of theory and practice, the detail and variance in the patient cases, and the subgroup analyses between EU and US neurosurgeons and academic versus non-academic centers.

Conclusions and future directions

This survey demonstrates the heterogeneity in local practices and preferences between surgeons and centers with regard to decision making and treatment modality selection in GBM patients. The lack of objective data and clinical guidelines has caused global variability since no consensus has been reached on a wide array of critical perioperative decisions. A large

consistency however between factors influencing the theoretical and practical decision-making exercises has been demonstrated. The results of this study mark the importance for additional research that addresses critical aspects of these processes. Further research could focus on the use of machine learning to create an algorithm incorporating the most important preoperative factors (e.g. location and eloquence, age, KPS, NIHSS) from which the optimum strategy in each case would be rendered (e.g. biopsy, debulking, maximum resection with or without mapping). This would serve as a tool for neurosurgeons to help them with their decision making. It would also be interesting to correlate the findings from this survey with responses from anesthesiologists and trained assessors of eloquent areas such as neuro-linguists and neurophysiologists. A third potential topic would be the difference in decision making in low-income versus high-income countries and its effect on best practices.

The current study may serve as a first step towards future large-scale research efforts to identify essential factors that can be optimized and may therefore benefit from consensus, consequently streamlining the decision-making process. This will provide the neurosurgical field with the required quantity, quality and depth of data on which practical guidelines can be based in order to focus on identifying the optimal treatment for subgroups of GBM patients.

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DATA SUPPLEMENT

Table S1: Baseline characteristics

Characteristic	Number of responses (%) (*n* = 212)
Gender	
Male	202 (90.2)
Female	22 (9.8)
Region (World Health Organization)	
American Region – United States/Canada	83 (37.1)
American Region – Latin America	17 (7.6)
European Region	91 (40.6)
Eastern Mediterranean Region	7 (3.1)
South-East Asia Region	10 (4.5)
Western Pacific Region	11 (4.9)
African Region	5 (2.2)
Institute	
Academic practice/University hospital	141 (62.9)
Non-academic practice/Community hospital	43 (19.2)
Private practice	32 (14.3)
Other	8 (3.6)
Training level	
Consultant neurosurgeon, >5 years of experience	185 (82.6)
Consultant neurosurgeon <5 years of experience	30 (13.4)
Neurosurgical fellow	8 (3.6)
Other	1 (0.4)
Total number of glioma resections performed	
<100	55 (24.6)
100-500	115 (51.3)
>500	54 (24.1)

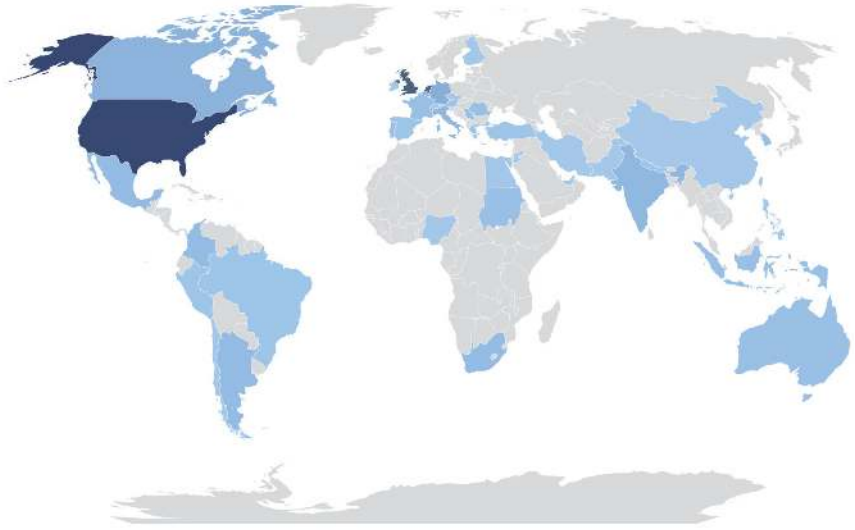

Figure S1: Survey respondents by country

Table S2: General decision making in GBM patients

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
Are neuro-oncology patients discussed in one or more dedicated multidisciplinary neuro-oncology tumor board(s)? *n*=224	• Yes	182 (81.3)[a]	$_{a/b}$<0.0001*	8.05 (2.14-30.31)	0.0021*	2.43 (0.71-8.37)	0.1587
	• No	33 (14.7)[b]					
	• No answer	9 (4.0)					
[Q: Multidisciplinary tumor boards: YES, *n*=182]: What is/are the timing of this/these multidisciplinary tumor board(s)? (select one or more answers)	• Before the patient is seen at the outpatient clinic	81 (44.5)[c]	$_{a/b}$<0.0001* $_{a/c}$<0.0001*	0.94 (0.45-1.97)	0.8669	4.78 (2.41-9.51)	<0.0001*
	• After the patient has been seen at the outpatient clinic	98 (53.8)[b]	$_{a/d}$<0.0001* $_{b/c}$<0.0764	1.61 (0.81-3.22)	0.1781	0.95 (0.50-1.80)	0.8794
	• After the definitive histopathological diagnosis	141 (77.5)[a]	$_{b/d}$<0.0035* $_{c/d}$<0.2460	1.63 (0.70-3.77)	0.2567	0.28 (0.12-0.69)	0.0051*
	• When requested by the patient's treating physician	70 (38.5)[d]		1.35 (0.67-2.75)	0.4018	1.08 (0.56-2.05)	0.8233
	• Other	4 (2.2)		NA		NA	
Please indicate on a Likert scale of 1-5 if the given factors influence your decision when choosing a treatment modality. *n*=189	• Location and eloquence	Mean 4.3 (SD=1.20)	NA	Est. -0.60 (SE=0.21)	0.0058*	Est. -0.014 (SE=0.20)	0.9462
	• Patient functioning (e.g. KPS)	Mean 4.2 (SD=0.99)		Est. -0.36 (SE=0.19)	0.0442*	Est. 0.36 (SE=0.17)	0.0355*
	• Preoperative neurological morbidity	Mean 4.0 (SD=0.98)		Est. -0.25 (SE=0.16)	0.1307	Est. 0.25 (SE=0.16)	0.1126
	• Patient's preference	Mean 3.8 (SD=1.20)		Est. -0.38 (SE=0.21)	0.0638	Est. 0.30 (SE=0.20)	0.1356
	• Comorbidities (e.g. ASA)	Mean 3.6 (SD=1.07)		Est. -0.24 (SE=0.19)	0.1989	Est. 0.32 (SE=0.18)	0.0760
	• Age	Mean 3.4 (SD=1.22)		Est. -0.17 (SE=0.21)	0.4201	Est. -0.063 (SE=0.20)	0.7526
	• Preoperative tumor size	Mean 3.0 (SD=1.20)		Est. -0.25 (SE=0.21)	0.2261	Est. -0.026 (SE=0.20)	0.8951
	• Patient's social circumstances	Mean 2.6 (SD=1.26)		Est. -0.63 (SE=0.22)	0.0045*	Est. -0.083 (SE=0.21)	0.6964

Table S2: General decision making in GBM patients (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
[Q: Age as a factor: score 4 or 5, *n*=97]: Why does the patient's age play a role in your decision making? (select one or more answers)	• Increasing risk of anesthesiologic or surgical complications with increasing age	67 (69.1)[b]	$_{a/b}$<0.4319 $_{a/c}$ 0.0001* $_{a/d}$<0.0001*	2.35 (0.80-6.86)	0.1185	1.04 (0.36-3.00)	0.9359
	• Increasing risk of neurological complications with increasing age	46 (47.4)[c]	$_{b/c}$<0.0022* $_{b/d}$<0.0001*	3.31 (1.14-9.65)	0.0283*	0.73 (0.27-1.98)	0.5422
	• The treatment's goals differ for younger and older GBM patients	72 (74.2)[a]	$_{c/d}$<0.0001*	0.95 (0.31-2.93)	0.9334	1.06 (0.37-3.07)	0.9083
	• Older patients prefer a biopsy more often	16 (16.5)[d]		1.57 (0.40-6.15)	0.5166	0.42 (0.12-1.54)	0.1925
	• Other	4 (4.1)		NA		NA	
[Q: Age as anfactor: score 4 or 5, *n*=97]: Above which value would the patient's age guide you towards choosing a biopsy rather than a resection?	• 60 years old	3 (3.1)[d]	$_{a/b}$ 0.0669	Overall		Overall	
	• 70 years old	25 (25.8)[b]	$_{a/c}$ 0.0014*	Est. 1.20 (SE=1.51)	0.4298	Est. -0.027 (SE=1.44)	0.9850
	• 75 years old	17 (17.5)[c]	$_{a/d}$<0.0001*				
	• 80 years old	37 (38.1)[a]	$_{b/c}$ 0.1616				
	• 85 years old	8 (8.2)[d]	$_{b/d}$ 0.0003*				
	• 90 years old	6 (6.2)[d]	$_{c/d}$ 0.0200				
	• No answer	1 (1.0)					
[Q: Age as a factor: score 1,2, or 3, *n*=82]: Why does the patient's age <u>not</u> influence your decision?	• GBM patients of all ages can benefit from tumor resection. Therefore, other factors are more important in deciding on surgical modality.	73 (89.0)[a]	$_{a/b}$<0.0001*	NA		NA	
	• Very few GBM patients can benefit from tumor resection. Therefore, other factors are more important in deciding on surgical modality.	6 (7.3)[b]		NA		NA	
	• Other	4 (4.9)		NA		NA	

Table S2: General decision making in GBM patients (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
Which statement do you agree most strongly with? *n*=186	• The impact of a resection in GBM patients is still highly debatable and therefore one should be very restrained in general to operate them. Biopsy or chemoradiotherapy only are usually the best choices.	3 (1.6)[c]	$_{a/b}$<0.0001* $_{a/c}$<0.0001* $_{b/c}$<0.0001*	NA		NA	
	• In older patients, the risk of morbidity outweighs de potential survival benefit: biopsy followed by adjuvant therapy is usually the best choice.	46 (24.7)[b]		0.59 (0.26-1.32)	0.2009	1.16 (0.52-2.59)	0.7086
	• In older patients, the patient's age should be approached relatively since performance and fitness are ultimately more important: resection followed by adjuvant therapy is usually the best choice.	133 (71.5)[a]		1.69 (0.76-3.80)	"	0.86 (0.39-1.91)	"
	• Other	4 (2.2)		NA		NA	

Table S2: General decision making in GBM patients (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
Please indicate whether the factors below would warrant a more aggressive (resection) or defensive (biopsy) surgical approach. *n*=114	• Large preoperative tumor volume						
	o Resection	87 (76.3)[a]	$_{a/b}$<0.0001*	2.17 (0.67-6.98)	0.1956	0.95 (0.29-3.05)	0.9268
	o Biopsy	3 (2.6)[c]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	24 (21.1)[b]	$_{b/c}$<0.0001*	0.45 (0.13-1.55)	0.2045	1.07 (0.31-3.76)	0.9115
	• Superficial location						
	o Resection	111 (97.4)[a]	$_{a/b}$<0.0001*	NA		NA	
	o Biopsy	0[c]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	3 (2.6)[b]	$_{b/c}$ 0.0838	NA		NA	
	• Deep location						
	o Resection	11 (9.6)[c]	$_{a/b}$<0.0001*	1.49 (0.32-6.93)	0.6151	0.94 (0.22-4.09)	0.9349
	o Biopsy	91 (79.8)[a]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	12 (10.5)[b]	$_{b/c}$ 0.8216	0.95 (0.29-3.10)	0.9291	0.67 (0.20-2.17)	0.5007
	• Midline location						
	o Resection	21 (18.4)[c]	$_{a/b}$<0.0008*	2.56 (0.62-10.62)	0.1964	1.77 (0.47-6.63)	0.3939
	o Biopsy	59 (51.7)[a]	$_{a/c}$<0.0001*	0.99 (0.39-2.51)	0.9892	0.89 (0.35-2.22)	0.7947
	o Neutral	34 (29.8)[b]	$_{b/c}$ 0.0446	0.59 (0.22-1.61)	0.3038	0.81 (0.30-2.22)	0.6865
	• In or near eloquent areas						
	o Resection	26 (22.8)[c]	$_{a/b}$ 0.1733	1.30 (0.47-3.57)	0.6090	0.43 (0.15-1.18)	0.1008
	o Biopsy	49 (43.0)[a]	$_{a/c}$<0.0012*	0.75 (0.28-2.00)	0.5682	0.22 (0.081-0.57)	0.0020*
	o Neutral	39 (34.2)[b]	$_{b/c}$ 0.0571	0.77 (0.28-2.11)	0.6090	2.34 (0.85-6.49)	0.1008
	• Near important nerves or blood vessels						
	o Resection	36 (31.6)[b]	$_{a/b}$<0.0048*	1.50 (0.55-4.12)	0.4319	1.85 (0.69-4.97)	0.2196
	o Biopsy	21 (18.4)[c]	$_{a/c}$<0.0001*	0.72 (0.21-2.48)	0.6067	0.67 (0.19-2.30)	0.5205
	o Neutral	57 (50.0)[a]	$_{b/c}$ 0.0217	0.85 (0.33-2.16)	0.7291	0.73 (0.29-1.82)	0.4936

Table S2: General decision making in GBM patients (continued)

Question	Response options	Overall response (%)	*P* value	Adjusted OR for academic vs. non-academic and private practice (95% CI)	*P* value	Adjusted OR for European vs. US neurosurgeons (95% CI)	*P* value
	• In or near basal ganglia						
	o Resection	0[c]	$_{a/b}$<0.0001*	NA		NA	
	o Biopsy	96 (84.2)[a]	$_{a/c}$<0.0001*	2.03 (0.52-7.92)	0.3057	0.77 (0.20-3.01)	0.7083
	o Neutral	18 (15.8)[b]	$_{b/c}$<0.0001*	0.49 (0.13-1.91)	"	1.30 (0.33-5.07)	"
	• Presence of cysts						
	o Resection	91 (79.8)[a]	$_{a/b}$<0.0001*	3.20 (0.97-10.60)	0.0566	0.87 (0.27-2.84)	0.8142
	o Biopsy	0[c]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	23 (20.2)[b]	$_{b/c}$<0.0001*	0.31 (0.094-1.03)	"	1.15 (0.35-3.77)	"
	• Multifocality						
	o Resection	10 (8.8)[c]	$_{a/b}$<0.0001*	NA		NA	
	o Biopsy	92 (80.7)[a]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	12 (10.5)[b]	$_{b/c}$ 0.6645	NA		NA	
	• Proximity to ventricles						
	o Resection	49 (43.0)[b]	$_{a/b}$ 0.7963	1.18 (0.47-2.98)	0.7196	1.12 (0.45-2.79)	0.8033
	o Biopsy	14 (12.3)[c]	$_{a/c}$<0.0001*	NA			
	o Neutral	51 (44.7)[a]	$_{b/c}$<0.0001*	1.14 (0.46-2.87)	0.7733	1.12 (0.45-2.76)	0.8121
	• Causing raised ICP						
	o Resection	111 (97.4)[a]	$_{a/b}$<0.0001*	NA		NA	
	o Biopsy	2 (1.8)[b]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	1 (0.9)[c]	$_{b/c}$ 0.5569	NA		NA	
	• Causing obstructive hydrocephalus						
	o Resection	106 (93.0)[a]	$_{a/b}$<0.0001*	NA		NA	
	o Biopsy	3 (2.6)[c]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	5 (4.4)[b]	$_{b/c}$ 0.4604	NA		NA	
	• Causing significant midline shift						
	o Resection	110 (96.5)[a]	$_{a/b}$<0.0001*	NA		NA	
	o Biopsy	2 (1.8)[b]	$_{a/c}$<0.0001*	NA		NA	
	o Neutral	2 (1.8)[b]	$_{b/c}$ 1.0000	NA		NA	

Legend: ASA = American Society of Anesthesiologists score. GBM: Glioblastoma Multiforme. ICP: Intracranial Pressure. KPS = Karnofksy Performance Score. OR: Odds Ratio.

Table S3: Survey responses specified by surgeon's experience

Question	Response options	<100 glioma resections performed (%)23	100-500 glioma resections performed (%)32	>500 glioma resections performed (%)22	*P* value
Please indicate on a Likert scale of 1-5 if the given factors influence your decision when choosing a treatment modality. *n*=189	• Location and eloquence	Mean 4.6 (SD=0.47)	Mean 4.4 (SD=1.25)	Mean 3.9 (SD=1.50)	NA
	• Patient functioning (e.g. KPS)	Mean 4.2 (SD=0.93)	Mean 4.2 (SD=1.01)	Mean 4.1 (SD=1.14)	
	• Preoperative neurological morbidity	Mean 4.0 (SD=0.76)	Mean 3.9 (SD=0.99)	Mean 4.0 (SD=0.99)	
	• Patient's preference	Mean 3.7 (SD=1.19)	Mean 4.1 (SD=1.11)	Mean 3.8 (SD=1.21)	
	• Comorbidities (e.g. ASA)	Mean 3.7 (SD=1.00)	Mean 3.5 (SD=0.98)	Mean 3.5 (SD=1.22)	
	• Age	Mean 3.5 (SD=1.08)	Mean 3.4 (SD=1.18)	Mean 3.2 (SD=1.19)	
	• Preoperative tumor size	Mean 3.4 (SD=1.04)	Mean 2.9 (SD=1.19)	Mean 3.8 (SD=1.21)	
	• Patient's social circumstances	Mean 2.4 (SD=1.25)	Mean 2.8 (SD=1.25)	Mean 2.5 (SD=1.29)	
[Q: Age as a factor: score 4 or 5, *n*=97]: Why does the patient's age play a role in your decision making? (select one or more answers)	• Increasing risk of anesthesiologic or surgical complications with increasing age	20 (87.0)	19 (59.4)	15 (68.2)	0.6497
	• Increasing risk of neurological complications with increasing age	10 (43.5)	13 (40.6)	14 (63.6)	
	• The treatment's goals differ for younger and older GBM patients	16 (69.6)	23 (71.9)	17 (77.3)	
	• Older patients prefer a biopsy more often	2 (8.7)	8 (25.0)	3 (13.6)	
	• Other	1 (4.3)	3 (9.4)	3 (13.6)	
[Q: Age as anfactor: score 4 or 5, *n*=97]: Above which value would the patient's age guide you towards choosing a biopsy rather than a resection?	• 60 years old	0	0	0	0.8230
	• 70 years old	7 (17.9)	5 (8.6)	5 (9.8)	
	• 75 years old	4 (10.3)	8 (13.8)	3 (5.9)	
	• 80 years old	7 (17.9)	13 (22.4)	10 (20.6)	
	• 85 years old	2 (5.1)	4 (6.9)	2 (3.9)	
	• 90 years old	3 (7.7)	2 (3.4)	1 (2.0)	
	• No answer	16 (41.0)	26 (44.8)	30 (58.8)	

Table S3: Survey responses specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)23	100-500 glioma resections performed (%)32	>500 glioma resections performed (%)22	*P* value
[Q: Age as a factor: score 1,2, or 3, *n*=82]: Why does the patient's age <u>not</u> influence your decision?	• GBM patients of all ages can benefit from tumor resection. Therefore, other factors are more important in deciding on surgical modality.	13 (86.7)	23 (92.0)	22 (95.7)	0.4599
	• Very few GBM patients can benefit from tumor resection. Therefore, other factors are more important in deciding on surgical modality.	2 (13.3)	1 (4.0)	0	
	• Other	0	1 (4.0)	1 (4.3)	
Which statement do you agree most strongly with? *n*=186	• The impact of a resection in GBM patients is still highly debatable and therefore one should be very restrained in general to operate them. Biopsy or chemoradiotherapy only are usually the best choices.	0	1 (1.7)	2 (3.9)	<0.0001*
	• In older patients, the risk of morbidity outweighs de potential survival benefit: biopsy followed by adjuvant therapy is usually the best choice.	13 (33.3)	43 (55.2)	37 (72.5)	
	• In older patients, the patient's age should be approached relatively since performance and fitness are ultimately more important: resection followed by adjuvant therapy is usually the best choice.	25 (64.1)	13 (22.4)	9 (17.36)	
	• Other	1 (2.6)	1 (1.7)	3 (5.9)	

Table S3: Survey responses specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)23	100-500 glioma resections performed (%)32	>500 glioma resections performed (%)22	*P* value
Please indicate whether the factors below would warrant a more aggressive (resection) or defensive (biopsy) surgical approach. *n*=114	• Large preoperative tumor volume				
	o Resection	23 (82.1)	23 (76.7)	23 (85.2)	0.9665
	o Biopsy	0	2 (6.7)	0	
	o Neutral	5 (17.9)	5 (16.7)	4 (14.8)	
	• Superficial location				
	o Resection	27 (93.1)	30 (100.0)	28 (100.0)	0.9650
	o Biopsy	0	0	0	
	o Neutral	2 (6.9)	0	0	
	• Deep location				
	o Resection	6 (20.7)	1 (3.3)	2 (7.1)	0.1576
	o Biopsy	23 (79.3)	26 (86.7)	22 (78.6)	
	o Neutral	0	3 (10.0)	4 (14.3)	
	• Midline location				
	o Resection	6 (20.7)	4 (2.5)	4 (14.3)	0.5976
	o Biopsy	17 (58.6)	17 (92.5)	13 (46.4)	
	o Neutral	6 (20.7)	8 (5.0)	11 (39.3)	
	• In or near eloquent areas				
	o Resection	7 (24.1)	6 (20.0)	8 (28.6)	0.4351
	o Biopsy	13 (44.8)	16 (53.3)	8 (28.6)	
	o Neutral	9 (31.0)	8 (26.7)	12 (42.9)	
	• Near important nerves or blood vessels				
	o Resection	7 (24.1)	10 (33.3)	12 (44.4)	0.1555
	o Biopsy	8 (27.6)	5 (16.7)	1 (3.6)	
	o Neutral	14 (48.3)	15 (50.0)	14 (50.0)	
	• In or near basal ganglia				
	o Resection	0	0	0	0.9543
	o Biopsy	26 (89.7)	25 (83.3)	25 (89.3)	
	o Neutral	3 (10.3)	5 (16.7)	3 (10.7)	

Table S3: Survey responses specified by surgeon's experience (continued)

Question	Response options	<100 glioma resections performed (%)23	100-500 glioma resections performed (%)32	>500 glioma resections performed (%)22	*P* value
	• Presence of cysts				
	o Resection	1 (3.4)	26 (86.7)	23 (82.1)	0.6956
	o Biopsy	27 (93.1)	0	0	
	o Neutral	1 (3.4)	4 (13.4)	5 (17.9)	
	• Multifocality				
	o Resection	1 (3.4)	6 (20.0)	0	0.1040
	o Biopsy	27 (93.1)	22 (73.3)	25 (89.3)	
	o Neutral	1 (3.4)	2 (6.7)	3 (10.7)	
	• Proximity to ventricles				
	o Resection	14 (48.3)	15 (50.0)	10 (35.7)	0.7815
	o Biopsy	1 (3.4)	2 (6.7)	2 (7.1)	
	o Neutral	14 (48.3)	13 (43.3)	16 (57.1)	
	• Causing raised ICP				
	o Resection	29 (100.0)	28 (93.3)	27 (96.4)	0.9757
	o Biopsy	0	2 (6.7)	0	
	o Neutral	0	0	1 (3.6)	
	• Causing obstructive hydrocephalus				
	o Resection	27 (93.1)	28 (93.3)	25 (89.3)	0.9612
	o Biopsy	1 (3.4)	1 (3.3)	1 (3.6)	
	o Neutral	1 (3.4)	1 (3.3)	2 (7.2)	
	• Causing significant midline shift				
	o Resection	28 (96.6)	28 (93.3)	28 (100.0)	0.9761
	o Biopsy	0	2 (6.7)	0	
	o Neutral	1 (3.4)	0	0	

Legend: ASA = American Society of Anesthesiologists score. GBM: Glioblastoma Multiforme. ICP: Intracranial Pressure. KPS = Karnofksy Performance Score. OR: Odds Ratio.

CHAPTER 14

Letter to the Editor:

The European and North American Consortium and Registry for Intraoperative Stimulation Mapping (ENCRAM): Framework for a Transatlantic Collaborative Research Initiative

Jasper K.W. Gerritsen, Marike L.D. Broekman, Steven De Vleeschouwer, Philippe Schucht, Brian V. Nahed, Mitchel S. Berger, Arnaud J.P.E. Vincent

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Dear Editor,

The European and North American Consortium and Registry for Intraoperative Stimulation Mapping (ENCRAM) is a transatlantic research alliance established in 2019.

The Consortium is chartered to advance European-North American neurosurgical scientific collaboration efforts and serve as a platform for bringing together a broad base of neurosurgeons and researchers investigating the application of intraoperative stimulation mapping (ISM) techniques (e.g. awake craniotomy) in glioma patients.

ENCRAM's focus is on collecting, analyzing and reporting clinical data in these patients. Its objectives include the following:

- Facilitate collaborative research in the field of ISM techniques in glio(blasto)ma patients between centers, countries and continents
- Develop expert consensus around patient selection, subgroup identification and surgical management of glioma patients
- Author papers in these niche areas, pioneering large-scale (randomized) clinical trials and (prospective and retrospective) cohort studies

The first project in which the Consortium will play a major role is the PROGRAM-study: an international, multicenter prospective non-randomized clinical trial of high-grade glioma resections using awake craniotomy and intraoperative stimulation mapping. The study includes neurosurgical centers in both Europe and the United States and is open for additional centers to participate.

We welcome colleagues involved in the (surgical) treatment of glioma patients to add their expertise to the Consortium's activities, thereby working collaboratively to enhance ISM-related research projects and build a transatlantic neurosurgical scientific bridge.

CHAPTER 15

The PROGRAM-study: awake mapping versus asleep mapping versus no mapping for high-grade glioma resections: study protocol for an international multicenter prospective 3-arm cohort study

Jasper K.W. Gerritsen, Marike L.D. Broekman, Steven De Vleeschouwer, Philippe Schucht, Christine Jungk, Sandro M. Krieg, Brian V. Nahed, Mitchel S. Berger, Arnaud J.P.E. Vincent

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ABSTRACT

Introduction

The main surgical dilemma during glioma resections is the surgeon's inability to accurately identify eloquent areas when the patient is under general anesthesia (GA) without mapping techniques. Intraoperative stimulation mapping (ISM) techniques can be used to maximize extent of resection in eloquent areas yet simultaneously minimze the risk of postoperative neurological deficits. ISM has been widely implemented for low-grade glioma resections (LGG) backed with ample scientific evidence, but this is not yet the case for high-grade glioma (HGG) resections. Therefore, ISM could thus be of important value in HGG surgery to improve both surgical and clinical outcomes.

Methods and Analysis

This study is an international, multicenter, prospective 3-arm cohort study of observational nature. Consecutive HGG patients will be operated with awake mapping, asleep mapping or no mapping with a 1:1:1 ratio. Primary endpoints are: 1) proportion of patients with NIHSS (National Institute of Health Stroke Scale) deterioration at 6 weeks, 3 months and 6 months after surgery and 2) residual tumor volume of the contrast-enhancing and non-contrast-enhancing part as assessed by a neuroradiologist on postoperative contrast MRI scans. Secondary endpoints are: 1) overall survival (OS) and 2) progression-free survival (PFS) at 12 months after surgery; 3) onco-functional outcome and 4) frequency and severity of Serious Adverse Events (SAEs) in each arm. Total duration of the study is 5 years. Patient inclusion is 4 years, follow-up is 1 year.

Ethics and Dissemination

The study has been approved by the Medical Ethics Committee (METC Zuid-West Holland/ Erasmus Medical Center; MEC-2020-0812). The results will be published in peer-reviewed academic journals and disseminated to patient organisations and media.

INTRODUCTION

Gliomas are the most common malignant tumors of the central nervous system (CNS) and are classified into grades 1-4, where grade 1 and -2 consist of low-grade gliomas (LGG) and grades 3 and -4 represent high-grade gliomas (HGG)[1,2]. Gliomas are relatively rare (incidence of 5/100,000 persons/year in Europe and North America), but are associated with a relatively high morbidity and mortality regardless of years of scientific efforts to improve clinical outcomes in these patients[1-7].

Studies show that maximizing the extent of resection of the contrast-enhancing part – and recently, the non-contrast-enhancing part as well – results in improved patient survival rates[8-15]. Moreover, patients with gross-total resections (GTR) derived the most benefit from the adjuvant chemoradiotherapy compared to patient with subtotal resections[16]. However, in excess of 50% of gliomas are located in- or near eloquent areas of the brain[2]. Eloquent areas are important areas within the brain where speech and/or motor functions are located. Damaging these areas during surgery can lead to severe and permanent neurological deficits that seriously impact the quality of life. As a consequence of this worsened condition, some patients are excluded for radio- and chemotherapy, leading to suboptimal clinical outcomes[16].

Thus, the main surgical problem for the surgeon is the inability to accurately identify these eloquent areas when the patient is under general anesthesia (GA) when no brain mapping techniques are being used. Surgeons often choose a more defensive approach for tumors that are located in or near these areas to prevent postoperative neurological deficits in patients with an already poor prognosis[2,10,12-15]. The use of intraoperative stimulation (neurophysiological) mapping techniques (ISM) can be necessary to enable the surgeon to resect as much tumor as possible while preserving quality of life and neurological functioning in these patients[17]. Mapping of motor-eloquent tumors can be performed while the patient is awake or asleep, while speech mapping can only be performed when the patient is awake. The use of mapping techniques has tremendous potential in glioma resections in eloquent areas, especially for HGG patients. However, there is currently no international consensus regarding the use of these techniques. The scientific evidence for the use of these techniques in this patient group is currently both inconclusive and fragmented. We therefore propose an international, multicenter prospective cohort study in which the use of awake and asleep mapping techniques in HGG patients will be evaluated.

The described research initiative will be able to study these techniques in a prospective setting while covering a breadth of centers and countries. Hence, the data generated in this ENCRAM research collaboration will be able to answer multiple research questions with

excellent generalizability, external validity and overall quality in both a cost-effective and practical setting[18].

METHODS AND ANALYSIS

Study design

This is an international, multicenter, prospective, 3-arm cohort study (registration: clinicaltrials.gov ID number NCT04708171). Eligible patients are operated using awake mapping, asleep mapping or no mapping with a 1:1:1 ratio with a sequential computer-generated random number as subject ID. Patients with motor-eloquent tumors will be treated in all study arms, while speech-eloquent tumors will only be treated in either the awake mapping or no mapping arm. The PROGRAM study is similar to the SAFE-trial (awake craniotomy versus craniotomy under general anesthesia for glioblastoma patients, NCT03861299) and is initiated by the same center, however, the presented study will be different in various ways: the PROGRAM study (1) will be an observational, prospective cohort study, (2) will include asleep mapping as an additional treatment arm, (3) will evaluate the extent of resection of the non-contrast-enhancing part of the tumor as well, (4) will include both WHO grade III and grade IV gliomas, (5) will include an onco-functional score as one of the outcomes, and (6) will include neurosurgical centers in the United States and is part of the ENCRAM Research Consortium[18].

Study objectives

The primary study objective is to evaluate the safety and efficacy of resections with or without mapping techniques (neurological morbidity and extent of resection) in HGG patients as expressed by NIHSS scores and volumetric data. Secondary study objectives are to study the overall survival (OS), progressive-free survival (PFS) and onco-functional outcome after resections with or without mapping techniques as expressed by survival data, progression on MRI scans and combining postoperative EOR/NIHSS outcomes respectively.

Study setting and participants

Patients will be recruited for the study from the neurosurgical or neurological outpatient clinic or through referral from general hospitals of the participating neurosurgical hospitals, located in Europe and the United States. The study is open to additional participating neurosurgical centers.

Patient and public involvement statement

Patients enrolled in the SAFE-trial (awake craniotomy versus craniotomy under general anesthesia for glioblastoma patients, NCT03861299) were consulted for this study to include patient experiences with resections with- and without mapping.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Age ≥18 years and ≤90 years
2. Tumor diagnosed as HGG (WHO grade III/IV) on MRI as assessed by the neurosurgeon
3. Tumors situated in or near eloquent areas; motor cortex, sensory cortex, subcortical pyramidal tract, speech areas or visual areas as indicated on MRI (Sawaya Grading II and II)[19]
4. The tumor is suitable for resection (according to neurosurgeon)
5. Written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Tumors of the cerebellum, brainstem or midline
2. Multifocal contrast enhancing lesions
3. Medical reasons precluding MRI (e.g. pacemaker)
4. Inability to give written informed consent
5. Secondary high-grade glioma due to malignant transformation from low-grade glioma
6. Second primary malignancy within the past 5 years with the exception of adequately treated in situ carcinoma of any organ or basal cell carcinoma of the skin

Interventions

(1) Awake craniotomy with local anesthesia (arm 1: awake mapping).

On the evening before surgery 1.5–2.0 mg lorazepam is administered for anxiolysis and 2x8 mg dexamethason. The patient is sedated with a bolus injection of propofol (0.5–1 mg/kg) and kept sedated with a propofol infusion pump (mean: 4 mg/kg/h) and remifentanil ((0.5-2 μg/kg/min). Supplemental O_2 might be provided through a nasal cannula. Patients typically receive 1-2 g of cefazolin and sometimes up to 1 g/kg of mannitol (all verified with the surgeon). The room is kept warm and patient covered as the goal is to have the core temperature above 36 C° during motor mapping. An arterial line (with standard monitoring for vital signs in addition to BP monitoring), central venous catheter, and urinary catheter are inserted. The patient is awakened and positioned on the table. At this point local anaesthesia

for the fixation of the head in the Mayfield clamp and the surgical field is provided with a mixture of 10 mL lidocaine 2% with 10 mL bupivacaine 0.5% plus adrenaline 1:200,000 for the Mayfield clamp and up to 40 mL bupivacaine 0.375% with adrenaline 1:200,000 for the surgical field. After positioning, clamp fixation, and surgical field infiltration, patients are sedated again for the trephination until the dura mater is opened, after local application of some drops of local anaesthetics. Propofol sedation is stopped after opening of the dura, with the patient awakening with as few external stimuli as possible. Cortical stimulation is performed with a bipolar electrical stimulator. The distance between both poles is 5 mm, and stimulation is performed by placing this bipolar pincet directly on the cortical surface and stimulating with increasing electrical biphasic currents of 2–12 mA (1-2 mA increasing steps, pulse frequency 60 Hz, single pulse phase duration of 100 microsec.) until motor or speech arrest is observed. For motor mapping a 2-second train and for speech mapping a 5-second train is used, respectively. The Boston naming test and repetition of words is done in cooperation with a neuropsychologist/linguist, who will inform the neurosurgeon of any kind of speech arrest or dysarthria. The difference between these is not always clear, but can be distinguished from involuntary muscle contraction affecting speech. When localizing the motor and sensory cortex, the patient is asked to report any unintended movement or sensation in extremities or face. Confirmed functional cortical areas are marked with a number. After completion of cortical mapping, a resection of the tumour is performed as radical as possible using an ultrasonic aspirator (CUSA) and suction tube, while sparing these functional areas. When the tumour margins or white matter is encountered or when on regular neuronavigation the eloquent white matter tracts are thought to be in close proximity, subcortical stimulation (biphasic currents of 8–16 mA, 1-2 mA increasing steps, pulse frequency 60 Hz, single pulse phase duration of 100 microsec., 2-second train) is performed to localize functional tracts. If subcortical tracts are identified, resection is stopped. During the resection of the lesion close to an eloquent area, the patient is involved in a continuous dialogue with the neuropsychologist. That way the neurosurgeon has 'online'-control of these eloquent areas. In case of beginning disturbances of communication or of motor or sensory sensations the resection is cessated immediately. When, due to stimulation, an epileptic seizure occurs, this is stopped by administering some drops of iced saline on the just stimulated cortical area.. If a seizure continues, an i.v. propofol or diphantoin bolus of 0.5 mg/kg is administrated and repeated until the seizure stops. The mapping procedure is temporarily halted. If the patient is adequate, cooperative and able to carry out tasks after the seizure, the mapping procedure can continue. In the case of refractory seizures, the mapping procedure will be permanently halted and the resection will continue under general anesthesia. After resection of the tumour a final neurological examination is performed. During closure of the surgical field the patient is sedated with propofol again. After wound closure and dressing, sedation is stopped. The awake patient is

transferred to the post-anaesthesia care unit (PACU), where the patient is hemodynamically and neurologically monitored for 24 hours.

(2) Asleep mapping under general anesthesia (arm 2: asleep mapping).

UCSF protocol: An IV is started on ipsilateral hand to the tumor. The patient is premedicated with up to 2 mg of midazolam. None if altered mental status (prevent further increase in ICP). Arterial (ipsilateral to tumor) catheter is inserted after induction of anesthesia. Anesthesia goals are to decrease ICP (if high), to maintain adequate CPP (at least 70 mmHg) to prevent cerebral ischemia from brain retraction, and to allow intraoperative cortical motor mapping. Patients typically receive 1-2 g of cefazolin, and 4 mg of decadron before skin incision, and sometimes up to 1 g/kg of mannitol (all verified with the surgeon). The room is kept warm and patient covered as the goal is to have the core temperature above 36 C° during motor mapping. Induction with propofol. In case of increased ICP, have patient hyperventilate during preoxygenation and continue hyperventilation with mask as soon as possible after induction of anesthesia. Fentanyl up to 5 μg/kg in divided doses throughout induction, prior to intubation. Adequate neuromuscular blockade (rocuronium) is verified prior to intubation to avoid coughing/straining. Eyes are taped, and at least one additional large bore IV is inserted. Neuromuscular relaxation is let to wear off for motor mapping (do not reverse). Patient position will depend on location of tumor. Anesthesia is mainained with 70% nitrous oxide in oxygen, low dose inhalation agent (less than 0.5 MAC), and a remifentanil (0.2 μg/kg/min) or fentanyl infusion (2 μg/kg/hr). Euvolemia is maintained (Lactated Ringer's). Mild hyperventilation (PaCO2 35 mmHg) is used. Once the bone flap is removed, the surgeon assesses the tightness of the dura. ICP is further decreased if necessary (pCO2, mannitol, propofol, head up etc.). Once the dura is open, the goal is to avoid brain shift so that stereotactic navigation system can be used optimally. During motor mapping, the arm, leg and face are uncovered to observe for movement. Stimulation is performed with the use of evoked potentials and continuous dynamic mapping/direct subcortical stimulation (CDM/DSS) with a monopolar stimulator (INOMED© Medizintechnik GmBH, Germany). During stimulation, TES-MEP registration is performed of the contralateral m. orbicularis oris, m. orbicularis oculi, m. biceps brachii, m. abductor pollicis, m. rectus femoris and m. tibialis anterior; and the ipsilateral m. abductor pollicis. SSEP registration is performed of the contralateral n. tibialis and bilateral n. medianus. The pulse form is negative, with 5 pulses and a pulse width of 500 μs, ISI 4 and current between 5-20 mA. In case of poststimulation continuation of motor activity, the surgeon will try to stop it by applying cold saline on the cortex. Have propofol (10 mg/ml) in line in case of intraoperative seizures (0.5 mg/kg for seizure suppression). May use neuromuscular relaxants after the last motor mapping. Fentanyl infusion is usually stopped at the beginning of closure. Remifentanil infusion is stopped about 10 min before end of surgery. At this point, use of inhalation agent may be replaced with a propofol infusion (50-100 μg/kg/min). pCO2 is normalized to facilitate

spontaneous breathing at the end of the operation. Use of inhalation agents (or propofol) is usually stopped about 10-15 min before end of surgery, and nitrous oxide at the end of surgery. Residual neuromuscular blockade is reversed once the Mayfield pins have been removed. At the end of the procedure all anaesthetics are stopped and patient is brought to the Post Anaesthesia Care Unit (PACU/IC). Detubation of the patient is performed as early as possible, if patient fulfils the detubation criteria (> 36 C body temperature, stable hemodynamics, sufficient spontaneous ventilation, adequate response to verbal orders). Postoperative analgesia is provided with paracetamol i.v. or p.o. 1 g up to 4 dd and morphine 7.5 mg s.c. up to 4 dd, if necessary. At the post-anesthesia care unit (PACU) the patient is hemodynamically and neurologically monitored for 24 hours.

Bern protocol: the following details are different to the above-mentioned protocol. Total intravenous anesthesia without inhalation agents is used (TIVA-only). A bolus of propofol is started (1–2mg/kg body weight) with fentanyl (1–2 mg/kg body weight), and remifentanil (1–2 mg/kg body weight) and maintained with propofol (100–200 mg/kg/min) and remifentanil (0.5 mg/kg/h). A short-acting relaxant is used (Esmeron 0.6 mg/kg body weight for the purpose of intubation. Then, the "train-of-four" technique is used involving percutaneous stimulation of the right median nerve (40 mA, 0.2- msec pulse duration) to test recovery from muscle relaxation. MEPs are recorded from subdermal electrodes in order to quantify the evoked responses. A combination of DCS MEP via a four-contact strip electrode placed on the pre-central gyrus for focal and selective stimulation and a back-up TES MEP via scalp electrodes is used[20]. The "suction probe" (INOMED medizintechnik, Germany; #525 650)" is used for cortical mapping and subcortical continuous dynamic mapping[21]. For subcortical stimulation a monopolar cathodal pulse stimulation is used with train of 5 pulses of 0.5 msec duration, ISI 4 msec and 2 Hz repetition rate. The mapping intensities range from 20 mA down to 3 mA (and in selective cases down to 1mA). Monitoring motor function is continued until dura closure in order to detect vascular injuries (for instance due to vasospasms).

(3) Craniotomy under general anaesthesia without mapping (arm 3: no mapping).

On the evening before surgery 1.5–2.0 mg lorazepam is administered for anxiolysis. 60 min. before anaesthesia induction the patient receives 1g paracetamol p.o. and 7.5-15 mg midazolam p.o. if requested for sedation. En route to the operating room, 0.5-2 mg midazolam i.v. may be given. 1g cefazoline is given iv. for antibiotic prophylaxis before anaesthesia induction. General anaesthesia is induced intravenously with fentanyl 0.25-0.5 mg, propofol 100-200 mg and cis-atracurium 10-20 mg. After induction of anaesthesia, patient is orotracheally intubated and mechanical ventilation is applied. Respiratory rate and tidal volume are adjusted to keep the patient normocapnic.

An arterial line (alternatively: two peripheral i.v.'s), central venous catheter (v. basilica), and urinary catheter are inserted. Anaesthesia is maintained with propofol (up to 10 mg/kg/h) and remifentanil (0.5-2 μg/kg/min). isoflurane (up to 1 MAC) and clonidine (1-2 μg/kg) may be added for maintenance, if necessary (a beta blocker or calcium channel blocker may be used to control BP as an alternative to clonidine). The fluid management is aiming for normovolemia. 0.9% saline solution and balanced crystalloids are used for maintenance, in case of blood loss > 300 ml, HAES 130/0.4 solution will be given. Temperature management is aiming for normothermia, warm-air blankets and warmed infusion lines are used. Arterial blood gas analysis is performed at the beginning of the procedure and repeated, if necessary. Electrolytes are controlled and substituted and hyperglycemia will be treated with insulin, if necessary. The anesthetized patient is positioned on the table. Local infiltration of the scalp is performed with 20 ml lidocaine 1% with adrenaline 1:200.000 to reduce bleeding. The insertion points of the Mayfield clamp are not infiltrated with local anaesthetics.

Trephination and tumour resection are performed without any additional neuro-psychological monitoring, guided by standard neuronavigation. At the end of the procedure all anaesthetics are stopped and patient is brought to the post-anesthesia care unit (PACU). Detubation of the patient is performed as early as possible, if patient fulfils the detubation criteria (>36 C body temperature, stable hemodynamics, sufficient spontaneous ventilation, adequate response to verbal orders). Postoperative analgesia is provided with paracetamol i.v. or p.o. 1 g up to 4 dd and morphine 7.5 mg s.c. up to 4 dd, if necessary. At the PACU the patient is hemodynamically and neurologically monitored for 24 hours.

Surgical adjuncts and additional imaging

The use of fMRI, DTI (Diffusion Tensor Imaging), ultrasound or 5-ALA is allowed to be used in all groups on the surgeon's indication.

Participant timeline

The flow diagram illustrates the main study procedures, including follow-up evaluations (Figure 1). In summary, study patients are allocated to either the awake mapping, asleep mapping or no mapping group and will undergo evaluation at presentation (baseline) and during the follow-up period at 6 weeks, 3 months, 6 months and 12 months postoperatively. Motor function will be evaluated using the NIHSS (National Institute of Health Stroke Scale) and MRC (Medical Research Council) scales. Language function will be evaluated using a standard neurolinguistic test-battery consisting of the Aphasia Bedside Check (ABC), Shortened Token test, Verbal fluency, Picture description and Object naming. Cognitive function will be assessed using the Montreal Cognitive Assessment (MOCA). Patient functioning with be assessed with the Karnofsky Performance Scale (KPS) and the ASA (American Society of Anesthesiologists) physical status classification system. Health-

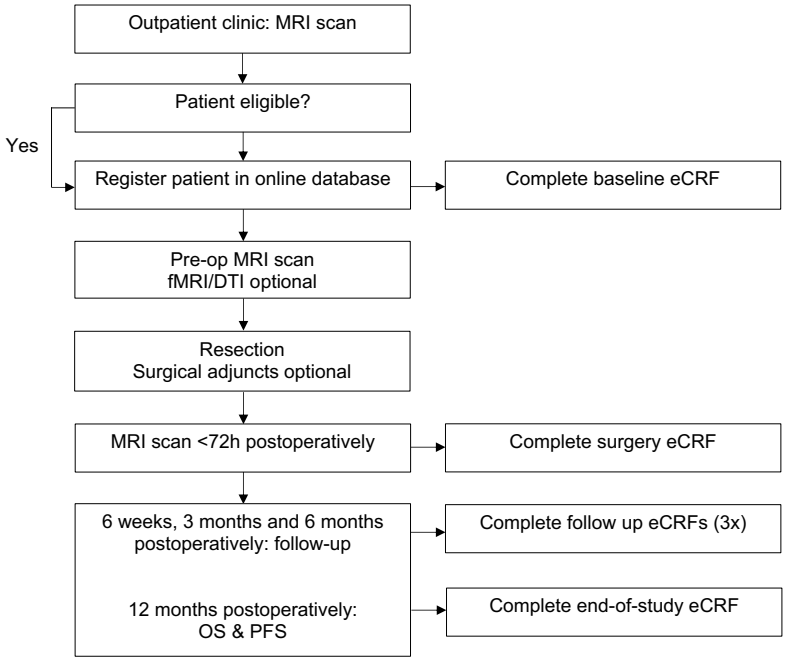

Figure 1: Study flowchart

related quality of life (HRQoL) will be assessed with the EQ-5D questionnaire and the QLQ-C30 and QLQ-BN20 questionnaires. Overall survival and progression-free survival will be assessed at 12 months postoperatively. We expect to complete patient inclusion in 4 years. The estimated duration of the study (including follow-up) will be 5 years.

Study procedures: Clinical evaluations and follow-up

- Pre-op (baseline) CRF
  - Unique subject ID, demographics (centre, year, gender, age), tumor specific factors (tumor volume pre-op, tumor hemisphere and lobe; eloquent areas), patient specific factors: preoperative KPS, ASA score, neurological status (NIHSS), MRC grade arm/leg (for motor-eloquent tumors), neurolinguistic testing, MOCA, EQ-5D, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D).
- Surgery CRF
  - Type of ISM, surgeon's rationale for modality, surgeon's goal, use of preoperative steroids (if yes: clinical improvement, conversion to mapping possible); use of surgical adjuncts (if DTI: integrity of tracts), use of additional imaging, radiological factors: resection percentage (both the contrast-enhancing and non-contrast-enhancing part), residual volume and postoperative ischemia.

- Follow-up CRFs
  - 6 weeks postoperatively: histology and molecular markers (WHO grade, MGMT status, IDH-1 status), neurological status (NIHSS), MRC grade arm/leg, status MRC arm/MRC leg/facialis/speech/visual (new, worsened, improved, stable), KPS, MOCA, EQ-5D, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D).
  - 3 months postoperatively: neurological status (NIHSS), MRC grade arm/leg, status MRC arm/MRC leg/facialis/speech/visual (new, worsened, improved, stable), KPS, neurolinguistic testing, MOCA, EQ-5D, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D).
  - 6 months postoperatively: neurological status (NIHSS), adjuvant treatment, MRC grade arm/leg, status MRC arm/MRC leg/facialis/speech/visual (new, worsened, improved, stable), KPS, MOCA, EQ-5D, QoL questionnaires (QLQ-C30, QLQ-BN20, EQ-5D).
  - 12 months postoperatively: progression-free survival, overall survival (end-of-study).

Outcomes

Primary outcome measures

The primary outcomes are 1) proportion of patients with NIHSS (National Institute of Health Stroke Scale) deterioration at 6 weeks, 3 months and 6 months postoperatively; deterioration is defined as an increase of at least one point on the total NIHSS score compared to this score at baseline and 2) residual tumor volume of the contrast-enhancing and non-contrast enhancing part, as assessed by a neuroradiologist on postoperative T1 with contrast MRI scan sequences using manual or semi-automatic volumetric analyses (Brainlab Elements iPlan CMF Segmentation, Brainlab AG, Munich, Germany; or similar software).

Secondary outcome measures

The secondary outcomes are 1) progression-free survival (PFS) at 12 months defined as time from diagnosis to disease progression (occurrence of a new tumor lesions with a volume greater than 0.175 cm^3, or an increase in residual tumor volume of more than 25%) or death, whichever comes first; 2) overall survival (OS) at 12 months defined as time from diagnosis to death from any cause; 3) onco-functional outcome defined as the calculated coordinate of the EOR on the x-axis and the postoperative NIHSS deterioration on the y-axis and 4) frequency and severity of Serious Adverse Events (SAEs) in each arm.

NIHSS

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke, but has

been used extensively for outcome in glioma surgery because of the lack of such scale for neuro-oncologic purposes and has been validated. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42 and the minimum score 0.

Aphasia Bedside Check (ABC)

ABC is a short screening test to detect aphasic disturbances at language comprehension and language production level at the main linguistic levels. It consists of 14 items in total. The cut-off score for signs of aphasia is ≤12.

Shortened Token Test

The shortened Token Test is a test for language comprehension and for the severity of a language disorder. The patient is asked to point and to manipulate geometric forms on verbal commands. It consists of 36 items. The cut-off score is 29.5.

Verbal fluency (category and letter)

Category and letter fluency are tests to assess flexibility of verbal semantic and phonological thought processing, semantic memory and concept generation. The patients is asked to produce words of a given category (animals, professions) or beginning with a given letter (D, A, T) within a limited time span.

Picture description and object naming

This is a subtest from the CAT-NL to assess semi-spontaneous speech in an oral and written way (5 minutes each condition). Scoring can be done according to the manual or more thoroughly according to the variables mentioned by Vandenborre et al[22]. To assess word retrieval, various object naming tests are used: BNT (Boston Naming Test), DuLIP (Dutch Linguistic Intraoperative Protocol) and VAN-POP (Verb and Noun test for Perioperative Testing).

Montreal Cognitive Assessment (MOCA)

The MOCA is a cognitive screening test to detect mild impairments across several cognitive domains; attention, verbal memory, language, visuo-constructive skills, conceptual thought, calculation and orientation. The total score is 30, the cut-off score is ≤ 26.

EQ-5D

The EQ-5D is a standardized questionnaire to assess the general health-related quality of life (HRQoL) in five domains: mobility, self-care, usual activity, pain/discomfort and anxiety/

depression. It is developed by the EuroQol Group and can also be used to calculate quality-adjusted life years (QALYs) for cost-utility analyses.

QLQ-C30 and QLQ-BN20

The QLQ-C30 and QLQ-BN20 are standardized questionnaires that have been designed by the Euoprean Organisation for Research and Treatment of Cancer (EORTC). They are used to assess the quality of life in cancer patients in general (C30) and brain tumor patients (BN20) by incorporating functional scales (physical, role, cognitive, emotional, social) and symptom scales (fatigue, pain, nausea and vomiting, seizures, communicating).

Sample size

This study has two primary endpoints. In order to guarantee that the overall type I error rate does not exceed 5%, we apply a weighted Bonferroni correction for multiple testing. The sample size calculations that follow take that into account. For the first primary endpoint, proportion of patients with neurological deterioration at 6 weeks post- surgery, we assume a deterioration rate of 10% in the control group (arm 3: no mapping), and 3% in the experimental groups (arm 1 and 2: awake and asleep mapping). A two-sample test for proportions with continuity correction requires 411 patients (137 per arm) in total in order to detect the above-mentioned difference of 7% with 80% power at a 4% significance level. For the second primary endpoint, proportion of patients without residual contrast-enhancing tumor on postoperative MRI, we assume a success rate of 25% in the control group (arm 3: no mapping), and 50% in the experimental groups (arm 1 and 2: awake and asleep mapping). A two-sample test for proportions with continuity correction requires 188 patients (94 per arm) in total in order to detect the above-mentioned difference of 25% with 80% power at a 1% significance level. In order to power the study for both primary endpoints, we should include the larger required number of patients, i.e. 411. A total of 411 eligible and evaluable patients in three arms allow the difference of 25% in proportion of patients without residual tumor to be detected with 88% power. Taking into account possible ineligibility and withdrawal of consent (we estimate this at 10%), a total of 453 patients will be included (151 patients per arm).

Data collection

All patient data is collected in the electronic data software Castor EDC. This software allows built-in logical checks and validations to promote data quality. Data entry and group allocation is performed by the study coordinator or locally by trained physicians and research nurses under supervision of the local investigator.

Data analysis

All analyses will be according the intention to treat principle, restricted to eligible patients. Patients initially registered but considered ineligible afterwards based on the histological analysis on tissue extracted during surgery, will be excluded from all analyses.

Primary study parameters

The primary endpoints will be analyzed using multivariate logistic regression. Subgroup analyses for tumor grade (WHO grade III/IV), molecular status, preoperative neurological morbidity, preoperative KPS, patient's age and tumor location/eloquence will be performed.

We will be including a stratification factor in the primary analysis model with each 10 observed events using the order of prognostic value as mentioned in the paragraph above, where the first 10 events will be used to estimate the effect of the arm. This rule will be applied in case less than 40 patients in total develop neurological deterioration. In the so constructed multivariate logistic regression model the treatment arm effect will be tested at 5% significance level. The primary analyses of proportion of patients without residual tumor and proportion of patients with postoperative deficits consist of a multivariate logistic regression, where arm effect is corrected for all minimization factors. In this model the group effect will be tested at 1% significance level. Manual or semiautomatic segmentation will be performed on axial T1 MRI Gadolinium contrast sequences and T2/FLAIR sequences to measure preoperative and postoperative volume of contrast-enhancing and non-contrast-enhancing part of the tumor, respectively. A determination of volumes will be calculated blinded for the treatment group.

Secondary study parameters

The Kaplan-Meier method will be used to estimate PFS and OS proportions per treatment group at appropriate time points, while the Greenwood estimate of the standard error will be used to construct the corresponding 95% CI. Multivariate cox proportional hazards models will be built for PFS and OS where treatment group effect will be corrected for minimization factors age, preoperative KPS (80 vs. 90 vs. 100), preoperative NIHSS (0-1 vs 2+), histopathological grading, molecular status, hemisphere and eloquence. Additionally, competing risk analysis will be used to calculate cumulative incidence of PFS (with competing risks progression/relapse and death without progression/relapse which add up to 100% at every time point). Onco-functional outcome will be evaluated using a scatter or bubble plot with volumetric data on the x-axis and neurological status (NIHSS) or patient performance (KPS) on the y-axis. SAEs in both groups will be described.

Study monitoring

No scheduled on-site monitoring visits will be performed. Local investigators will remain responsible for the fact that the rights and well-being of patients are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. No Data Safety Monitoring Board will be installed: all interventions are care-as-usual and patients are allocated without randomisation.

Adverse events (AEs) and serious adverse events (SAEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to neurosurgery. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded from start of surgery until 6 weeks after surgery. Serious adverse events are any untoward medical occurrence or effect that results in death; is life-threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgement by the investigator. An elective hospital admission will not be considered as a serious adverse event. Most of the (serious) adverse effects of treatments be mainly related to the surgery: post operative pain, nausea and anaemia (in case of massive blood loss), Infections, intracranial haemorrhage, epilepsy, aphasia, paresis/paralysis in arms or/and legs.

Most of the (serious) adverse effects of treatments (awake surgery or surgery under generalised anaesthesia) will be mainly related to the surgery: postoperative pain, nausea and anaemia (in case of massive blood loss), infections, intracranial haemorrhage, epilepsy, aphasia, paresis/paralysis in arms or/and legs. The neurological morbidity is under investigation in this trial and well-known risk / complications of the craniotomy and can be attributed to the nature of the operation. Neurosurgical clinics are well adapted to prevent and treat such events. SAEs will be collected through routine data management.

Publication of results

Trial results will be published in an international journal, communicated to neurological and neurosurgical associations and presented at (inter)national congresses.

Ethics and Dissemination

The study has been approved by the Medical Ethics Committee (METC Zuid-West Holland/ Erasmus Medical Center; MEC-2020-0812) and is conducted in complicance with the European Union Clinical Trials Directive (2001/20/EC) and the principles of the Declaration of Helsinki (2013). The results of the study will be published in peer-reviewed academic journals and disseminated to patient organisations and media.

DISCUSSION

Neurosurgeons face a major dilemma during glioma surgery: maximizing extent of resection while minimizing risk of postoperative neurological deficits. The use of awake or asleep mapping techniques has the potential to equip the surgeon intraoperatively with the needed information to balance these two surgical goals.

A substantial amount of evidence is available on the usefulness of awake mapping to increase resection percentage while preserving quality of life in low-grade glioma patients[23-34]. In contrast, only very few studies have reported the use of awake mapping in high-grade glioma patients, although this technique could be of important value in these patients as well[17,23, 25-27,34]. Recent retrospective evidence showed that glioblastoma patients operated with awake mapping had significant less postoperative neurological morbidity and significantly higher percentage of total resections[35,36]. In patients with motor-eloquent tumors, the use of asleep mapping techniques with evoked potentials or continuous dynamic mapping can be a viable alternative to preserve these functional tracts[20,21,37,38].

There is a clear need for solid prospective evidence of the use of these techniques in HGG patients. The presented international neurosurgical research consortium will provide the needed infrastructure to perform ongoing large-scale data collection[18]. This study aims to evaluate whether the use of awake or asleep mapping is the appropriate answer to the surgeon's surgical dilemma during high-grade glioma resections. Furthermore, it will be the first to directly compare awake and asleep mapping techniques in their ability to improve patient outcomes for neurological morbidity, quality of life and survival. Last, using various multivariate analyses, there will be an additional focus on identifying the best surgical choice in subgroups of high-grade glioma patients.

Trial status

The study will start at April 1st, 2021 and is open to additional participating neurosurgical centers.

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CHAPTER 16

General discussion

GENERAL DISCUSSION

The overall aim of this thesis was to evaluate the impact of awake brain surgery in glioblastoma patients. In this final chapter, the results will be discussed in a broader context and potential implications for clinical practice and future research will be addressed. First, the assessment of clinical outcomes in glioblastoma patients will be discussed. Second, the impact of awake mapping will be evaluated and its effects on surgical safety, extent of resection, and survival for glioblastoma patients as a whole and for patient subgroups. Third, the current heterogeneity in surgical approaches and mapping procedures will be examined. Last, prospects for future scientific efforts and perspectives will be elaborated upon.

Assessment of surgical outcomes in glioblastoma surgery

Extent of resection (EOR) and residual tumor volume are two sides of the same coin and can be used as objective outcome measurements to assess tumor cytoreduction. Both have been associated with survival outcomes [1-10]. Residual tumor volume has been introduced rather recently and has been indicated to be a better predictor of survival outcomes than EOR [9,10]. In contrast with extent of resection, it is independent from preoperative tumor volume and therefore indicates the extent of cytoreduction in a more standardized manner which eases comparison of patient cohorts. Therefore, the current paradigm of reporting cytoreduction is shifting increasingly towards residual tumor volume, although extent of resection is still a widely accepted outcome measurement.

To complicate matters, there is yet no consensus about the quantitative definition of the concepts of partial resection, subtotal resection, near total resection, gross-total resection and supramaximal resection [13]. For gross-total resection, definitions in the literature ranged from 90-100% [14,15], 96-100% [16], 97-100% [17] to 100% [18-23], while for near-total resection the most commonly reported values were ≥ 95% EOR or ≤ 1 cm^3 (1 ml) residual volume [10, 23, 24]. Previous studies suggested that patients with tumor resections of ≥ 95% had better survival outcomes than patients with ≤ 95% EOR [11,16], but it remains virtually unknown if patients with for example, an EOR of 95-98% experience similar or different survival outcomes from patients with values above or under this range.

The generally accepted values with regard to minimum thresholds that would lead to distinctly improved survival outcomes are 80% (EOR) and 2-5 ml (residual volume) [4, 9, 10, 20], which we therefore used as cut-off points in our GLIOMAP study. Furthermore, we defined gross-total resection as 0.0-0.2 ml (0.0-0.2 cm^3) residual tumor volume (which is in line with the value used by Stummer *et al* [25] in their 5-ALA trial [0.175 ml/0.175 cm^3]), or an extent of resection of 98-100%, which is comparable with values that are used in previous studies [14-23].

A large number of studies still use the "raw" findings from the clinician's neurological examination to report neurological deficits in glioblastoma patients. Although this might be practical in the clinical setting, it may be ill-suited for scientific purposes because it hampers an objective comparison of neurological status between individual patients and cohorts. We therefore decided to use the National Institute of Health Stroke Scale (NIHSS) as the main instrument in our studies to assess preoperative and postoperative neurological performance. Originally, this grading scale has been designed to measure the clinical severity of stroke patients, but has proved to be a reliable outcome measurement in neuro-oncological studies as well [25-28]. Notably, the NIHSS score can be abstracted from medical records with a high degree of reliability and validity, which makes it a fine option for multicenter retrospective cohort studies [29]. Moreover, various options exist to assess patient functioning according to their activities of daily living. The most common options include the 11-grade Karnofsky Performance Score (KPS) [30-33], the 6-grade ECOG/WHO grading scale [34] and the 7-grade modified Rankin Scale (mRS) [35]. The KPS is the used frequently in glioma studies and therefore has an excellent inherent capacity for comparisons between institutes, cohorts and patients and is often standardly reported in the patient records. Consequently, we selected KPS as our main tool to measure overall patient functioning preoperatively and postoperatively.

Within the onco-neurosurgical scientific community, it is common practice to separately report outcomes that measure extent of resection and outcomes that measure neurological morbidity, patient functioning or quality of life. However, reporting these outcomes as two separate entities fails to adequately address the true purpose of glioma resections, and glioblastoma resections in particular: to optimize the "onco-functional outcome" in these patients. The ultimate goal of glioblastoma surgery is to optimize the extent of resection or residual volume while preventing the deterioration of the patient's neurological status or overall functioning. Often, the resection would only be considered a "true success" when both these goals have been achieved. It therefore follows that reporting the outcomes that represent these two goals separately would only be half the story, and a novel tool was necessary to strengthen the current arsenal [of outcome measures] in these patients. Combining two outcome measures – to address both surgical goals – could make the comparison of postoperative outcomes between patients and cohorts considerably more effective. We consequently decided to combine NIHSS/EOR and KPS/EOR into a merged onco-functional outcome (OFO). Hereby, a 2D coordinate is created for each individual patient in a two-dimensional *x,y* graph with a quantitative measurement of the oncological objective on one axis (EOR) and the functional objective on the other (NIHSS, KPS). We hypothesized that this would lead to the presentation of different subgroups of glioblastoma patients as a cluster of coordinates. However, when developing this grading scale, we acknowledged that postoperative NIHSS or postoperative KPS would not suffice, since such a measure-

ment would not take into account the preoperative status of the patient. By adding a "delta" (Δ, the net difference between the postoperative and preoperative scores) to the NIHSS and KPS values we made these measures independent from their respective preoperative values. We developed four different OFO models based on the data of three large university centers: ΔNIHSS-EOR and ΔKPS-EOR at 6 weeks and 6 months postoperatively. Patient clustering formed 5 distinct subgroups in both models: OFO 1a, OFO 1b, OFO 2, OFO 3a and OFO 3b. We identified OFO 1a and 1b as the subgroups with the best surgical outcome for both extent of resection and NIHSS/KPS. These patients experienced the highest extent of resections and had improved (OFO 1a) or stable (OFO 1b) postoperative NIHSS/KPS scores. Furthermore, they had the best survival outcomes of all subgroups. OFO 2 was an "in-between group" that consisted of patients that were very similar to patients in OFO 1a as for preoperative status, but did not receive adjuvant chemotherapy and radiotherapy as often as patients in OFO 1a and had a considerably lower median EOR. Last, we concluded that the subgroups OFO 3a and OFO 3b consisted of patients in whom one of the surgical goals was not achieved: maximizing extent of resection (OFO 3a) or preventing neurological deficits (OFO 3b), which consequently resulted in impeded survival outcomes.

The developed OFO grading scale is an excellent additional tool to measure surgical outcomes and will enable the clinicians and researchers to compare glioblastoma patients more effectively. This new grading scale should be validated in an external cohort and will be used as a new outcome measurements in our future studies, starting with the PROGRAM-study.

Awake mapping in glioblastoma patients

Awake brain mapping is a surgical technique for reducing postoperative deficits and increasing extent of resection in predominantly low-grade glioma patients. Over the last few years, it has been shown that awake mapping can be a useful tool in glioblastoma resections as well [36-47]. However, these studies included a mix of low-grade and high-grade glioma patients or focused on glioblastoma patients as a whole. Therefore, the exact impact of awake brain mapping in different patient subgroups is still unknown which severely hampers the assessment of surgical strategies and the indication setting of this technique. In order to summarize the available evidence in a quantitative manner, we performed a meta-analysis in which we focused on high-grade glioma patients in whom mapping techniques were used. According to the results of the meta-analysis, awake mapping was associated with a longer median overall survival, less postoperative neurological complications, and an increased incidence of gross-total resections. Furthermore, extent of resection and preoperative KPS were indicated as prognostic factors for survival outcomes, whereas preoperative KPS and an eloquent location of the tumor were identified as predictive factors for postoperative neurological complications. Data from our own patient series from the Erasmus MC between 2005-2015 confirmed that awake mapping was associated with a higher extent of

resection and less postoperative neurological complications, especially long-term deficits at 6 months postoperatively. However, in our series there was no survival benefit for the awake group. The GLIOMAP study, including patients from Rotterdam, The Hague, Leuven and Boston, supplied us with more precise answers. We found that awake mapping overall led to less neurological deficits at 3 months and 6 months, a higher extent of resection and a lower residual tumor volume, a longer overall survival, and a longer progression-free survival. Moreover, it was proved to be an independent predictor for receiving adjuvant chemotherapy and radiotherapy, gross-total resection based on residual tumor volume and gross-total resection based on extent of resection. These findings were in line with the results of our first retrospective study which had been carried out on a smaller scale. However, not all of these outcomes did not apply to all patient subgroups. The overall cohort had been divided in 6 subgroups based on age (< 70 vs ≥ 70), preoperative NIHSS score of (0-1 vs. ≥ 2) and preoperative KPS (90-100 vs. ≤ 80). Awake mapping led in all subgroups to a higher extent of resection and a lower residual tumor volume. This was confirmed with multiple multivariable regression analyses that indicated awake mapping as an independent predictor for reaching gross-total resection based on either 98-100% extent of resection or 0.0-0.2 ml residual tumor volume in all subgroups. Notably, these cytoreductive advantages in the awake group did only translate in improved overall survival and progression-free survival in patients aged < 70 years, with a preoperative NIHSS score of 0-1 or a preoperative KPS of 90-100, in particular after 18 months postoperatively. Since these survival benefits were especially pronounced in patients with MGMT methylated tumors, we hypothesize that the synergistic effect of the higher extent of resection due to awake mapping and the sensitivity to adjuvant therapy due to MGMT methylation may be the rationale behind these findings.

Gross-total resection was found to lower the risk of postoperative neurological deterioration independently. Furthermore, awake mapping led in the subgroups of age < 70, preoperative NIHSS score 0-1, preoperative NIHSS score ≥ 2, and preoperative KPS 90-100 to less postoperative neurological deficits at 3 months and 6 months. For patients in the subgroups of age ≥ 70 and KPS ≤ 80, awake mapping led to less postoperative neurological deficits only at 3 months or 6 months respectively.

The number of patients in the subgroups of age ≥ 70, NIHSS ≥ 2, and KPS ≤ 80 that have been operated with the use of awake mapping over the last 10 years was considerably lower than in the other subgroups. This has led to diminished power and precision in the performed analysis with regard to these subgroups. In the subgroups aged ≥ 70 or with a preoperative of KPS ≤ 80, we observed that awake mapping led to less neurological deterioration at 6 months postoperatively and a higher extent of resection (and a lower residual volume in the KPS ≤ 80 subgroup), irrespective of the patient's preoperative KPS or NIHSS scores. Therefore, prevention of these "late" neurological complications could be considered the

prime rationale for choosing awake mapping in these patients, since the increased EOR did not translate into improved outcomes for overall survival or progression-free survival. In patients with a preoperative NIHSS score of ≥ 2, awake mapping was not only useful for averting late neurological deterioration but also at 3 months postoperatively. Furthermore, it was predictive of receiving adjuvant chemotherapy and radiotherapy. Optimizing these patient's performance to undergo adjuvant therapy could therefore be seen as an important reason to consider awake mapping in these patients.

An important finding was the fact that patients aged ≥ 70 or patients with an impeded preoperative NIHSS score (≥ 2) or KPS (≤ 80) proved to have the most benefit from gross-total resection as indicated by the survival analyses and confirmed by the multivariate regression analyses. A closer look at the data might offer us a potential solution. We hypothesize that in younger patients (<70) or patients with a better preoperative status (NIHSS 0-1, KPS 90-100), factors other than volumetric data might carry a stronger prognostic value: preoperative KPS score and postoperative NIHSS and KPS scores in younger patients, preoperative NIHSS score in patients with a preoperative KPS of 90-100, and age and motor/language eloquence in patients with a preoperative NIHSS score of 0-1. We assume that for these patients, tumor cytoreduction is important (as indicated by the survival analyses), but preventing postoperative NIHSS and KPS worsening (<70 subgroup, NIHSS 0-1 subgroup) or optimizing preoperative neurological functioning (KPS 90-100 subgroup) might be of greater importance to improve survival outcomes. We therefore stress the importance of awake mapping in these subgroups to maintain optimum KPS and NIHSS scores, which in turn would benefit their survival by safeguarding the receipt of adjuvant chemotherapy and radiotherapy. Last, we found that 6-week NIHSS and 6-week KPS deterioration were of greater prognostic importance in the subgroups aged <70, NIHSS 0-1 and KPS 90-100 than in the subgroups aged ≥ 70, NIHSS ≥ 2 and KPS ≤ 80, suggesting that in the former subgroups surgical safety might be more important as a prognostic factor in overall survival, while removing as much of the tumor as possible is in the latter.

Heterogeneity in surgical approaches and mapping procedures

To validate the results of our retrospective studies in a prospective manner, we decided to launch the international multicenter PROGRAM-study. During the development phase of this cohort study, we noticed that the local mapping procedures between centers and differed considerably. The extent of this heterogeneity had never been assessed objectively, although certain aspects of the procedure may very well benefit from consensus, which might be advantageous for future collaborative efforts as well. Moreover, we found that the attitudes with regard to glioblastoma surgery and the selection of surgical modality in various cases covered the whole spectrum of defensive towards aggressive options. These observations were congruent with our experiences during the development and execution

of the SAFE-trial and are exemplary for the fact that the neurosurgical field is still divided on a number of key topics, examples of which are: how aggressive one should operate on glioblastoma patients, the added value of mapping techniques in glioblastomas in or near eloquent areas, and if one should be restrained with performing a resection among elderly glioblastoma patients (and instead should opt for more defensive options such as a biopsy).

We carried out two global surveys to objectively assess this assumed heterogeneity. The results of our first survey showed an evident amount of heterogeneity among surgeons and centers with respect to their local mapping procedures. Notable differences were observed for the kinds of equipment and settings that are used for both awake and asleep mapping, the intraoperative assessment of eloquent areas, the use of surgical adjuncts, the use of monitoring, the anesthesia management, the assessment of neurological morbidity and the perioperative decision making.

The findings of our second survey highlighted significant differences with respect to the local practices in the decision-making process as well as the treatment preferences of centers and surgeons in glioblastoma patients as a whole and in various patient cases. For example, not all institutes had installed a multidisciplinary neuro-oncology tumor board, whereas the timing of this board differed significantly between institutes who had. Moreover, there was no consensus among surgeons regarding the importance of various perioperative factors in the decision-making process, the role and meaning of various perioperative factors in this process (aggressive vs. defensive approach), the reasons why the patient's age does or does not play a role in this process and how aggressive the treatment for glioblastoma patients in general should be. Overall, location and eloquence of the tumor, and the preoperative neurological score and KPS were indicated to be the most important factors for surgeons on which they based their surgical strategy. These findings supported the way we had divided our cohort into subgroups for the GLIOMAP study. To test these theoretical preferences, a number of hypothetical patients were presented in which the cases differed in age, preoperative neurological morbidity, preoperative KPS, location and eloquence of the tumor, comorbidities and the patient's preference. We found that the preferred treatment in various glioblastoma cases differed significantly between surgeons. When case variants were presented with adaptations in the aforementioned factors, the adaptation of the preferred surgical strategy based on these variants was also significantly different. A particular finding was that the surgeon's reported importance of various perioperative factors does often correspond with their case responses: in the case variants, respondents who had earlier in the survey rated the factor or factors that were altered important in their decision were more likely to change their approach.

Surgical approaches and decision-making processes did not only differ between individual surgeons, but also between institutes and continents as well. Academic practices more often performed awake and asleep mapping procedures and more often employed a clinical neurophysiologist with telemetric monitoring. Furthermore, multidisciplinary boards were more common at academic centers.

There were significant differences in preference among European versus US neurosurgeons regarding the modality for cortical and subcortical mapping, the use of surgical adjuncts and anesthesia management for awake mapping. Besides, European neurosurgeons more commonly discussed the patient at multidisciplinary boards prior to the outpatient clinic. On the other hand, their American colleagues more commonly discussed the patient at these boards after the histopathological diagnosis, are less likely to perform a biopsy when the tumor is located in or near eloquent areas, and were generally more likely to have a slightly more aggressive surgical approach.

We performed these surveys as a first step towards a collaborative effort to investigate key variables that can be optimized and may therefore benefit from consensus, consequently streamlining the decision-making process. Such a project will provide the neurosurgical field with the required quantity, quality, and depth of data to identify the optimal treatment for subgroups of glioblastoma patients on which practical guidelines can be based.

Future perspectives

Investigating the impact of awake mapping in subgroups of glioblastoma patients – which is the only way to determine the optimal treatment in individual patients and potentially to re-assess surgical strategies – is solely possible with the use of large-scale datasets with sufficient power to generate high-level evidence. To achieve this, institutes have to collaborate and perform relevant, multicenter studies with a more sizable patient cohort. Single-center institutes are adequate for carrying out pilot studies, developing proof-of-concepts, and identifying scientific hiatuses. However, the translation from low-level evidence yielded from single-center studies towards validation of these findings in larger-scaled research efforts allows to formulate high-level evidence for critical clinical questions. The potential downsides of regularly developing and initiating large multicenter studies are differences in clinical practice between participating centers which could bias the results, as well as administrative and legal challenges. To tackle these challenges and to strengthen the scientific infrastructure between centers, we founded the ENCRAM Consortium. Such as Consortium has the advantage of allowing the research team to upscale from single-center to multi-center studies in a quick and efficient manner and to address new insights in spin-off studies. In this manner, a two-way street is created that enables partners to swift between the test hypotheses on a small scale and validate the concurrent findings on a large scale,

after which new hypotheses will emerge. Creating the infrastructure to initiate a similar research cycle was therefore one of the major objectives of this Consortium.

One of the new projects of the Consortium is the SUBTRACT study, which will evaluate the functional assessment of subcortical tracts during glioma surgery. The aim of this study is to develop a practical guideline for the preservation of specific subcortical tracts. There are a number of key questions that need to be addressed before consensus can be reached. Which settings have to be used during the intraoperative testing phase? What are the recommended neurological, cognitive and linguistic tests to perform, and for which specific functions? How will the preoperative, intraoperative and postoperative performance of various neurological domains be determined (motor, language, visual, sensory, cognitive)? Which deficits can be expected after surgery with the involvement of specific subcortical tracts and how should these potential deficits be assessed and quantified?

A second question is the role of awake mapping versus other mapping techniques for the resection of motor-eloquent gliomas. One of the Consortium's future projects will be the comparison of the awake and asleep mapping technique for motor-eloquent gliomas in the non-dominant hemisphere. The group in Bern advanced the asleep mapping technique towards continuous monitoring of the motor structures' integrity with a technique called continuous dynamic mapping (CDM). This technique utilizes a monopolar probe at the tip of the suction device. Thanks to the known current-distance relationship of monopolar stimulation, the surgeon can resect tumor tissue close to motor pathways with stepwise decreasing stimulation intensity, while continuously being guided by the different sounds of the device (indicating the distance to the motor fibers) [48,49]. CDM has been found to be a very safe, feasible, and intuitive alternative for conventional asleep mapping and awake mapping in order to prevent neurological deficits in motor eloquent gliomas. Though, it is yet unknown if these techniques are similar or different in their impact on postoperative outcomes. The PROGRAM-study will therefore include a third treatment arm, in which patients will be operated with the asleep CDM technique, which is already routinely used in the University Hospitals of Bern and Leuven with excellent results.

A third research effort should elucidate the added benefit of surgical adjuncts during awake mapping procedures. Stummer *et al* presented in 2006 the results of their well-known randomized controlled trial regarding the use of 5-aminolevulinic acid (5-ALA, a fluorescent agent) during glioma resections [25]. Since then, a large number of papers has investigated the impact of 5-ALA [50-58], but only Schucht *et al* [52] investigated the combination of 5-ALA and brain mapping in glioma patients.

Furthermore, there are promising but contradictory results regarding the use of intraoperative ultrasound in glioblastoma patients [59-71]. Studying the combined effect of 5-ALA and awake mapping or ultrasound and awake mapping in subgroups of glioblastoma patients would be of great value with potential implications for the indication setting of these techniques.

One of the most promising new awake mapping techniques includes functional ultrasound (fUS), which uses Doppler ultrasound images to detect changes in brain tissue perfusion as a result of task-induced brain activity. With fUS, the surgeon identifies eloquent areas based on a vascular, rather than a mechanical basis. Advantages of fUS include its high spatiotemporal resolution, wide field of view, high depth penetration and its low-cost of implementation. The Paris group described this technique in 2017 as a proof-of-principle in low-grade gliomas [72]. In 2020, the Rotterdam group published their results of using fUS during awake surgery for mapping motor and language function in low-grade and high-grade glioma patients [73]. The impact of fUS on postoperative outcomes in glioblastoma patients has yet to be investigated, as is the comparison between awake surgeries using electrocortical stimulation mapping versus fUS, adding fUS to the standard awake mappin regimen and the effect of fUS in subgroups of glioblastoma patients.

Last, a fourth question applies to the indication setting of awake mapping in glioblastoma patients and expanding the scope from primary tumors towards recurrent tumors as well. Various papers have focused on the resection's indication setting in these patients and the impact of extent of resection [16, 74-77]. However, evidence on the role of awake mapping in recurrent glioma patients specifically is much scarcer [78]. It would be very informative if the findings regarding the impact of awake mapping in primary glioblastoma patients also apply to recurrent glioblastoma patients. Recurrent patients could be divided in subgroups according to the same parameters that are used in the cohort of primary glioblastomas for the sake of outcome continuity and consequent ease of comparison. Ultimately, we have to determine for each individual glioblastoma patient the best possible surgical strategy while taking into account the combination of the patient's age, neurological morbidity, performance status and the location, eloquence, and genetic mutations of their tumor.

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CHAPTER 17

Summary
Nederlandse samenvatting
Dankwoord
Acknowledgements
PhD Portfolio
List of Publications
Curriculum Vitae

SUMMARY

Chapter 1 describes the aim of the thesis, in which the main research questions that will be answered are discussed and in which manner these questions should be addressed ideally.

Chapter 2 serves as the general introduction and consists of a literature review evaluating the recent advances and modern challenges of safe surgery in glioblastoma patients. It addresses the key surgical challenge of maximizing extent of resection while preventing neurological deficits. Furthermore, it elaborates on the various ways in which both goals can be achieved, with awake mapping being one of the most evident. Last, it presents an overview of the current prospective scientific efforts regarding maximum safe resection in glioblastoma patients.

Chapter 3 describes a meta-analysis that was performed to assess the impact of intraoperative stimulation mapping on high-grade glioma surgery outcome. After inclusion of 53 studies and 9102 patients it was found that awake mapping resulted in a longer overall median survival in glioblastoma patients as well as a higher rate of gross-total resections and less postoperative neurological complications. Furthermore, extent of resection and preoperative KPS were indicated as prognostic factors, whereas preoperative KPS and involvement of eloquent areas were predictive of postoperative neurological complications.

Chapter 4 is the response to a Letter to the Editor regarding the aforementioned meta-analysis that elaborates on the use and general potential benefit of awake mapping in glioblastoma surgery. Besides, it stresses the importance of studying its impact on postoperative outcomes such as survival, extent of resection and quality of life in subgroups of glioblastoma patients.

Chapter 5 presents the results of a single-center retrospective cohort study directly comparing awake mapping with asleep craniotomy in glioblastoma patients. The findings of this paper, based on a cohort of 405 patients, suggested that awake mapping led on average to a higher extent of resection and less long-term postoperative neurological complications without affecting overall survival.

Chapter 6 consists of a single-center retrospective study that evaluates the impact of dedicated neuro-anesthesia management on clinical outcomes in 401 glioblastoma patients. Dedicated neuro-anesthesia was found to lead to significantly less postoperative neurological complications, better fluid balance, shorter hospital length-of-stay and lower admission costs. Moreover, the combined appointment of a dedicated neuro-anesthesiologists and

oncological neurosurgeon led to less short-term and long-term neurological complications and increased extent of resection significantly.

Chapter 7 concerns the study protocol for the SAFE-trial, a multicenter randomized controlled trial that directly compares awake mapping with asleep resections in 246 patients from the Netherlands and Belgium. Primary outcomes are postoperative neurological deficits, proportion of patients with gross-total resections. Secondary outcomes are health-related quality of life, overall survival, progression-free survival and frequency and severity of Serious Adverse Events (SAEs). The trial commenced in April 2019 is scheduled for completion 5 years later in April 2024. As of now, 80 of the 246 patients have been included in the trial. This study is the first RCT to compare awake and asleep resections.

Chapter 8 is a Letter to the Editor commenting on the joint consensus of the SNO and EANO on the current management and future directions for glioblastoma patients. It emphasizes the value of assessing extent of resection and postoperative patient functioning and pioneers the idea of a merged 2D onco-functional outcome (OFO). Different subgroups of glioblastoma patients are hypothesized to form clusters of coordinates according to their OFO score which would enable clinicians and researchers to compare subgroups more effectively and in better alignment with the original aim of the resection.

Chapter 9 presents the proof-of concept of this OFO grading scale based on a multicenter cohort of patients from the Erasmus MC, Haaglanden MC and UZ Leuven. For each individual patient, a postoperative OFO coordinate can be created based on extent of resection (x-axis) and the pre-op/post-op difference (Δ) in neurological morbidity (NIHSS) or KPS at 6 weeks and 6 months postoperatively. Consequently, a 5-step OFO grading scale could be created and for each OFO grade it was demonstrated to represent different subgroups of glioblastoma patients indeed. Furthermore, the patient's OFO grading significantly impacted his or her survival outcomes.

Chapter 10 presents the results of the multicenter GLIOMAP study including a cohort of 4075 glioblastoma patients from the Erasmus MC, Haaglanden MC, UZ Leuven and Brigham and Women's Hospital. The study was set up to investigate the effect of awake mapping in subgroups of eloquent glioblastoma patients divided by age (<70 and ≥ 70 years), preoperative neurological morbidity (NIHSS score 0-1 and NIHSS score ≥ 2) and preoperative patient functioning (KPS 90-100 and KPS ≤ 80). The data demonstrated that awake mapping was independently associated with a higher extent of tumor resection, a lower residual volume, and a lower incidence of postoperative neurological deterioration in all patients. This translated into improved overall survival and progression-free survival

in patients aged <70 years, with a preoperative NIHSS score of 0-1 or a preoperative KPS of 90-100.

Chapter 11 describes a supplementary analysis of the GLIOMAP study that evaluates the value of extent of resection, residual tumor volume and gross-total resection (defined as 98-100% extent of resection or 0.0-0.2 ml residual tumor volume) in the overall cohort and across subgroups of glioblastoma patients. The study's results indicated that a higher extent of resection or lower residual tumor volume significantly improved survival outcomes for all subgroups except in the NIHSS 0-1 subgroup for overall survival and in the subgroups aged ≥ 70 and KPS 90-100 for progression-free survival. Gross-total resection was found to be especially beneficial for overall survival improvement in the subgroups aged ≥ 70, NIHSS score ≥ 2 and KPS ≤ 80 without increasing the risk of postoperative NIHSS or KPS worsening. In fact, an extent of resection of 98-100% significantly decreased the overall risk of neurological (NIHSS) deterioration at 6 weeks postoperatively, suggesting that gross-total resection can be pursued safely and could be even protective of postoperative neurological worsening.

Chapter 12 concerns a global survey that evaluates the heterogeneity in local mapping procedures across countries, centers and surgeons. The results showed that there were significant differences for the equipment and settings used during mapping procedures, the intraoperative assessment of eloquent areas, use of surgical adjuncts (e.g. fluorescence or ultrasound) and monitoring, anesthesia management, assessment of neurological morbidity and perioperative decision making.

Chapter 13 describes the results of a second global survey that examines the decision making and surgical modality selection in glioblastoma patients. Neurosurgeons were inquired about their decision-making process and the perioperative factors that would influence their surgical approach in glioblastoma patients (aggressive vs. defensive). Moreover, they were asked to elaborate on their preferred surgical modality in a number of patient cases, which varied significantly between countries and surgeons. We found that tumor location and eloquence, preoperative patient functioning and preoperative neurological morbidity were the most important factors on which the surgeon's approach was based which was confirmed in the practical cases.

Chapter 14 is a Letter to the Editor that announces the foundation of the European and North American Consortium and Registry for Intraoperative Mapping (ENCRAM). This Consortium is charactered to advance the transatlantic scientific collaboration efforts and serve as a platform for investigating the application of mapping techniques in glioma patients.

Chapter 15 concerns the study protocol for the PROGRAM-study, which is a 3-arm prospective cohort study that compares awake mapping, asleep mapping and no mapping in high-grade glioma patients from the Netherlands, Belgium, Germany, Switzerland and the United States. Primary outcomes are postoperative neurological deficits, residual volume of the contrast-enhancing and non-contrast-enhancing tumor. Secondary outcomes are overall survival, progression-free survival, onco-functional outcome and frequency and severity of Serious Adverse Events (SAEs). The study has commenced on February 2021 and is scheduled for completion 5 years later in February 2026.

Chapter 16 consists of the general discussion, in which the results that were presented in this thesis are discussed and the research questions that were posed in Chapter 1 are answered.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 beschrijft het doel van de thesis, waarbij wordt besproken welke onderzoeksvragen beantwoord trachten te worden en op welke manier dit idealiter uitgevoerd zou worden.

Hoofdstuk 2 dient als de algemene introductie en betreft een overzicht van de literatuur met betrekking tot de recente ontwikkelingen en huidige uitdagingen voor veilige chirurgie bij glioblastoom patiënten. Dit artikel gaat in op de belangrijke chirurgische uitdaging bij glioblastoom operaties: het maximaliseren van het resectiepercentage met tegelijkertijd het voorkomen van neurologische uitval na de operatie. Daarnaast worden de verschillende manieren waarop dit kan worden bereikt besproken, waarbij de wakkere operatie een van de meest evidente is. Tenslotte wordt er een overzicht gegeven van de huidige prospectieve studies die maximale veilige chirurgie bij glioblastoom patiënten onderzoeken.

Hoofdstuk 3 beschrijft een meta-analyse die werd uitgevoerd om het effect van "mapping" tijdens hooggradige glioom operaties op chirurgische uitkomsten te bestuderen. Na inclusie van 53 studies en 9102 patiënten werd geconcludeerd dat wakkere operaties leidden tot een langere algehele overleving en tot minder neurologische complicaties na de operatie. Bovendien waren resectiepercentage en KPS vóór de operatie prognostisch relevant, terwijl KPS en een eloquente locatie van de tumor predictief werden bevonden voor neurologische complicaties na de operatie.

Hoofdstuk 4 is een respons op een Brief aan de Editor met betrekking tot de hierboven genoemde meta-analyse waarbij het gebruik en de meerwaarde wordt besproken van de wakkere operatie bij glioblastoom patiënten. Bovendien wordt het belang benadrukt van het nader onderzoeken van de invloed van deze techniek op postoperatieve uitkomsten zoals overleving, resectiepercentage en kwaliteit van leven in subgroepen van glioblastoom patiënten.

Hoofdstuk 5 beschrijft de resultaten van een retrospectieve cohortstudie in het Erasmus MC waarbij de wakkere operatie wordt vergeleken met de slapende operatie bij glioblastoom patiënten. De bevindingen van dit artikel, dat gebaseerd is op een cohort van 405 patiënten, impliceren dat de wakkere operatie leidt tot gemiddeld een hoger resectiepercentage en minder postoperatieve neurologische complicaties op de lange termijn, zonder invloed te hebben op de overleving.

Hoofdstuk 6 betreft een retrospectieve cohortstudie in het Erasmus MC waarbij de impact van de neuro-anesthesie op de klinische uitkomsten bij 401 glioblastoom patiënten.

Neuro-anesthesie leidde op basis van deze resultaten tot significant minder postoperatieve neurologische complicaties, een betere vochtbalans, een kortere opnameduur in het ziekenhuis en lagere kosten. Bovendien leidde de gecombineerde toewijzing van een neuro-anesthesioloog en oncologische neurochirurg bij glioblastoom operaties tot minder neurologische complicaties op zowel de korte als de lange termijn en een hoger resectiepercentage.

Hoofdstuk 7 betreft het studieprotocol voor de SAFE-trial, een multicenter gerandomiseerd gecontroleerde studie (RCT) waarbij de wakkere operatie met de slapende operatie wordt vergeleken bij 246 patiënten uit Nederland en België. Primaire uitkomstmaten zijn postoperatieve neurologische uitval en het aandeel patiënten met een volledige resectie van de tumor. Secundaire uitkomstmaten zijn kwaliteit van leven, algehele overleving, progressie-vrije overleving en frequentie en ernst van ernstige bijwerkingen (SAEs). De trial is van start gegaan in April 2019 en staat gepland om 5 jaar later in April 2024 voltooid te worden. Op dit oment zijn er 80 van de 246 patiënten geïncludeerd in de trial. Deze studie is de eerste RCT die de wakkere met de slapende operatie vergelijkt.

Hoofdstuk 8 is een Brief aan de Editor waarop er gereageerd wordt op de bereikte consensus door de SNO en EANO met betrekking tot het huidige klinische behandelbeleid en de toekomstige richtingen voor onderzoek bij glioblastoom patiënten. Hierbij wordt de waarde benadrukt van het tezamen vaststellen van het resectiepercentage en postoperatieve functioneren van de patiënt en wordt het idee gepionierd van een samengestelde 2D onco-functionele uitkomst (OFO). De hypothese hierbij is dat verschillende subgroepen van glioblastoom patiënten een cluster van coördinaten vormen op basis van hun individuele OFO-score, wat clinici en onderzoekers in staat stelt om subgroepen patiënten effectiever met elkaar te vergelijken.

Hoofdstuk 9 beschrijft de proof-of-concept van deze OFO-gradering, gebaseerd op een multicenter cohort van patiënten van het Erasmus MC, Haaglanden MC en UZ Leuven. Voor elke individuele patiënt kan een postoperatieve OFO-coördinaat gecreëerd worden op basis van het bij deze patiënt bereikte resectiepercentage (x-as) en het pre-op/post-op verschil (Δ) in neurologische morbiditeit (NIHSS) of KPS op 6 weken en 6 maanden postoperatief. Op deze manier kan een OFO schaal met 5 graderingen worden gecreëerd en voorts werd aangetoond dat elke OFO-gradering inderdaad een afzonderlijke subgroep patiënten vertegenwoordigd. Bovendien werd aangetoond dat de OFO-gradering van de patiënt een significante invloed had op zijn of haar overleving.

Hoofdstuk 10 betreft de resultaten van de multicenter GLIOMAP-studie met betrekking tot 4075 glioblastoom patiënten van het Erasmus MC, Haaglanden MC, UZ Leuven en het Brigham and Women's Hospital. De studie was geïnitieerd om de impact te onderzoeken

van de wakkere operatie bij verschillende subgroepen glioblastoom patiënten die van elkaar verschilden op basis van leeftijd (<70 en ≥ 70 jaar), neurologische uitval vóór de operatie (NIHSS-score 0-1 en NIHSS-score ≥ 2) en functioneren van de patiënt vóór de operatie (KPS 90-100 en KPS ≤ 80). Er kon geconcludeerd worden dat de wakkere operatie onafhankelijk geassocieerd was met een hogere incidentie van complete tumorresecties bij alle patiënten en een lagere incidentie van neurologische verslechtering na de operatie bij alle patiënten. Dit vertaalde zich in een langere algehele- en progressie-vrije overleving bij patiënten <70 jaar, met een preoperatieve NIHSS score van 0-1 of een preoperatieve KPS van 90-100.

Hoofdstuk 11 beschrijft de resultaten van een aanvullende analyse van de GLIOMAP-studie waarbij de meerwaarde van resectiepercentage, residueel tumorvolume en volledige tumorresectie (gedefinieerd als 98-100% resectiepercentage of 0.0-0.2 ml residueel tumor volume) in het cohort patiënten in het algemeen en bij subgroepen patiënten. De resultaten van de studie lieten zien dat een hoger resectiepercentage of een lager residueel tumorvolume de overleving significant verbeterde bij alle subgroepen patiënten, behalve bij de NIHSS 0-1 subgroep voor algehele overleving en bij de subgroep van ≥ 70 jaar of KPS 90-100 voor progressie-vrije overleving. Totale tumorresectie was met name van waarde voor het verbeteren van de overleving bij patiënten van ≥ 70 jaar, met een NIHSS- score ≥ 2 of KPS ≤ 80 zonder dat hierbij het risico op NIHSS of KPS-verslechtering na de operatie toe nam. Integendeel, een resectiepercentage van 98-100% verminderde het risico op NIHSS-verslechtering op 6 weken postoperatief significant, wat suggereert dat totale tumorresectie veilig kan worden nagestreefd en zelfs beschermend kan zijn voor postoperatieve neurologische verslechtering.

Hoofdstuk 12 betreft een wereldwijde enquête waarbij de verschillen in lokaal gebruikte "mapping" technieken tussen landen, ziekenhuizen en neurochirurgen werd geïnventariseerd. De resultaten lieten zien dat er significante verschillen bestaan wat betreft het materiaal en de instellingen die gebruikt worden tijdens de "mapping" procedures, de wijze van het vaststellen van eloquente hersengebieden, het gebruik van chirurgische hulpmiddelen (zoals fluorescentie of echo) en monitoring, anesthesiologisch beleid, het vaststellen van neurologische uitval en operatieve beslisvorming.

Hoofdstuk 13 rapporteert over de resultaten van een tweede wereldwijde enquête die de beslisvorming en keuze voor een bepaalde chirurgische modaliteit bij glioblastoom patiënten evalueert. Neurochirurgen werden bevraagd aangaande hun proces van beslisvorming en de factoren die hun keuze sturen met betrekking tot het agressiever versus defensiever chirurgisch benaderen van glioblastoom patiënten. Bovendien werd hen gevraagd verder uit te wijden aangaande hun geprefereerde chirurgische benadering in een aantal patiënten casussen, die significant bleken te verschillen tussen landen en neurochirurgen onderling.

Locatie en eloquentie van de tumor, alsook functioneren en neurologische status van de patiënt vóór de operatie werden in theorie als meest belangrijke factoren bevonden waar de neurochirurg zijn of haar keuze voor chirurgische benadering op baseerde. Dit werd tevens bevestigd in de praktijk n.a.v. de keuzes bij de patiënten casussen.

Hoofdstuk 14 is een Brief aan de Editor waarbij de oprichting wordt aangekondigd van het Europese en Noord-Amerikaanse Consortium en Register voor Intraoperatieve Mapping (ENCRAM). Dit Consortium is bedoeld om de trans-Atlantische wetenschappelijke samenwerking te bevorderen en als een platform te dienen voor het onderzoek naar de toepassing van de "mapping" technieken bij glioom patiënten.

Hoofdstuk 15 betreft het studieprotocol voor de PROGRAM-studie: een 3-armige prospectieve cohortstudie waarbij "mapping" bij zowel wakkere als slapende operaties wordt vergeleken met operaties zonder het gebruik hiervan. De studie includeert hooggradige glioom patiënten in Nederland, België, Duitsland, Zwitserland en de Verenigde Staten. De primaire uitkomstmaten zijn postoperatieve neurologische uitvalsverschijnselen en residueel volume van het contrast aankleurende gedeelte en het niet-contrast aankleurende gedeelte van de tumor. De secundaire uitkomstmaten zijn algehele overleving, progressie-vrije overleving, onco-functionele uitkomst en frequentie en ernst van ernstige bijwerkingen (SAEs). De studie is van start gegaan in Februari 2021 en staat gepland om 5 jaar later in Februari 2026 afgerond te worden.

Hoofdstuk 16 bevat de algemene discussie, waarbij de eerder in dit proefschrift besproken bevindingen worden bediscussieerd en de initiële onderzoeksvragen worden beantwoord.

DANKWOORD

Graag zou ik dit proefschrift afsluiten met het bedanken van hen die van aanmerkelijk belang zijn geweest bij de totstandkoming van deze thesis. Zonder onderstaande personen was het simpelweg niet mogelijk geweest om deze marathon te volbrengen.

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Dr. Marike Broekman, als co-principal investigator van de SAFE-trial in Den Haag ben je van grote waarde geweest voor het (tot nu toe) succesvolle verloop van deze studie. Zonder jou waren de inclusies in het Haaglanden nooit zo vlot gegaan. Tevens wil ik je bedanken voor het beschikbaar stellen van jullie data voor de GLIOMAP-studie. Je stond altijd klaar om constructieve input te leveren op al die projecten, papers, revisies, en nieuwe ideeën die ik je voorlegde. Ontzettend bedankt hiervoor, ik heb veel van je geleerd – de week in Boston was memorabel.

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mede ontwikkelen van de onco-functionele uitkomst. Ik kijk ernaar uit de komende jaren met u te blijven samenwerken binnen het ENCRAM Consortium.

Leden van de grote commissie: prof. dr. Leenstra, dr. Geurts, dr. Wagemakers, hartelijk dank voor uw bereidheid tot deelname als opponent in de grote commissie.

Principal investigators van de SAFE-trial, dr. Fred Kloet en dr. Marike Broekman (Den Haag), dr. Geert-Jan Rutten (Tilburg), dr. Michiel Wagemakers (Groningen) en dr. Giorgio Hallaert (Gent): graag zou ik jullie willen bedanken voor het faciliteren van deze studie in jullie centra. De ontwikkeling, opzet en uitvoering van een multicenter RCT blijft een enorme opgave, die enkel volbracht kan worden door nauwe samenwerking.

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ENCRAM Consortium members: prof. dr. de Steven De Vleeschouwer (Leuven), prof. dr. Philippe Schucht (Bern), prof. dr. Sandro Krieg (Munich), dr. Christine Jungk (Heidelberg), dr. Brian Nahed (Boston), and dr. Mitchel Berger (San Francisco): thank you for putting your trust in this ambitious project. International, multicenter collaboration initiatives like ours might be the only way to gather such volumes of GBM data. I am looking forward to

work together with all of you for the years to come – our PROGRAM-study will be a big success.

Collega's van Na-21: Dana, Pablo, Wendy, Ellen, Saskia, Anne-Sophie en Marike, elke keer als ik de lift uitstapte op Na-21 was het weer een verrassing wie ik deze keer zou aantreffen. Het was me een genoegen om met jullie onze flexplek kantoortuin te delen. Dana en Ellen, dank voor al die keren dat ik mijn frustraties met jullie kon delen over de immer uitdijende, niet zelden zinloze bureaucratie. Door jullie stapte ik altijd weer vrolijker de lift in dan dat ik eruit kwam. Ik wens jullie allen veel succes met jullie mooie onderzoeksprojecten.

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PHD PORTFOLIO

Name PhD Candidate	J.K.W. Gerritsen
Department	Neurosurgery
PhD period	2018 – 2021
Title thesis	Awake Brain Surgery in Glioblastoma Patients
Promotoren	Prof. dr. C.M.F. Dirven
	Prof. dr. A.J.P.E. Vincent

PhD Training	Year	ECTS
Conferences and Presentations		
Wintermeeting NVVN (Veenendaal, NL)	2019	0.6
Scientific Meeting Dept. of Neurosurgery Erasmus MC (Rotterdam, NL)	2019	0.3
EANS Annual Scientific Meeting (Dublin, IE)	2019	2.0
AANS Annual Scientific Meeting (San Diego, CA, USA)	2019	2.0
Scientific Meeting NVVN (Utrecht, NL)	2018	0.3
Scientific Meeting Dept. of Neurosurgery Erasmus MC (Rotterdam, NL)	2018	0.3
CNS Annual Scientific Meeting (Houston, TX, USA)	2018	2.0
EANS Annual Scientific Meeting (Brussels, BE)	2018	2.0
Courses		
Personal Leadership and Communication	2021	1.0
Survival Analysis Course	2020	0.6
Basic Training LimeSurvey	2020	0.3
Biomedical English Writing	2020	2.0
Adobe Photoshop and Illustrator	2020	0.3
Basic Course on Regulations and Organization of Clinical Trials (eBROK)	2019	1.5
Scientific Integrity	2019	0.3
Systematic Literature Search PubMed	2018	0.3

Teaching		
Supervising Clinical Research Master Student	2020-	8.0
Supervising 2nd Year Medical Students (2)	2020-	8.0
Supervising 3th Year Medical Students (3)	2020-	8.0
Project coordination and grant writing		
The GLIOMAP-study (project leader, EU)	2020-	10.0
The BIOPSY-trial (KWF grant application, NL)	2020-	5.0
ENCRAM Consortium (project leader, EU/USA)	2019-	10.0
The PROGRAM-study (project leader, EU/USA)	2019-	10.0
The SAFE-trial (KWF grant application, NL/BE)	2018-	5.0
KNAW Van Walree Travel Grant	2019	1.0
Total		**80.8**

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1. **Gerritsen JKW,** Vincent AJPE. Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomized controlled trials. *Br J Sports Med.* 2016. 50(13):796-803
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4. **Gerritsen JKW**, Vincent AJPE. Response to Letter to the Editor: "Impact of intraoperative stimulation mapping in high-grade glioma surgery outcome: A meta-analysis". *Acta Neurochirurgica*. 2020. 162(2):429-31
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12. **Gerritsen JKW,** Zwarthoed RH, Versyck G, Pruijn K, Fisher FL, Larivière E, Solie L, Broekman MLD Vincent AJPE, De Vleeschouwer S. A novel postoperative onco-functional outcome (OFO) grading scale to assess extent of resection and postoperative patient functioning simultaneously to compare glioblastoma subgroups. *Under review, Neuro-Oncology.*
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15. **Gerritsen JKW,** Broekman MLD, De Vleeschouwer S, Schucht P, Nahed BV, Berger MS, Vincent AJPE. Letter to the Editor: The European and North American consortium and registry for intraoperative stimulation mapping (ENCRAM): Framework for a transatlantic collaborative research initiative. *Neurosurgery.* 2021. 88:E369. Doi: 10.1093/neuros/nyaa568
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CURRICULUM VITAE

Jasper Kees Wim Gerritsen was born in Tilburg (the Netherlands) on March 26, 1995. He grew up in Oisterwijk and graduated from the Theresialyceum (VWO Gymnasium). In 2013, he commenced his medical education at the Erasmus Medical Center (Erasmus University) in Rotterdam. During his first year of medical school, he started his research at the Neurosurgery department under supervision of dr. A.J.P.E. Vincent, focusing on the use of awake mapping techniques in glioblastoma patients. In 2018, they received funding from KWF Dutch Cancer Society (grant call 2018-II) to carry out an international multicenter randomized controlled trial (RCT) for investigating the impact of awake craniotomies in glioblastoma patients (the SAFE trial), for which he was appointed as study coordinator. He graduated from medical school *cum laude* in 2019 and began working on his PhD research full-time (promotor: prof. dr. C.M.F. Dirven, copromotor: dr. A.J.P.E. Vincent). Subsequently, he founded the European and North American Consortium and Research Alliance for Mapping procedures in glioma surgeries (ENCRAM), which includes centers from the Netherlands, Belgium, Germany, Switzerland, and the United States. The first project that has culminated from this Consortium has been the development of an international prospective multicenter cohort study, which investigates the impact of awake and asleep mapping techniques in high-grade glioma patients (the PROGRAM-study), for which he is currently appointed as principal investigator. In 2021, he started working as a resident-not-in-training (ANIOS) at the Erasmus' Department of Neurosurgery, and commenced his neurosurgical training as resident-in-training (AIOS) in 2022.