



Functional Mapping-Guided Resection of Eloquent Diffuse Low-Grade Gliomas: A Single-Institution Experience from a Low-Middle Income Country

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ABSTRACT

AIM: To report our experience in implementing functional mapping-guided resection for eloquent diffuse low-grade gliomas (DLGGs) in a low- and middle-income country (LMIC) setting. There are logistical barriers to achieving onco-functional balance through glioma surgery in LMICs.

MATERIAL and METHODS: The study is a retrospective chart review of adult patients who underwent surgical resection of their DLGGs that were located within supratentorial eloquent brain areas (within 15 mm). Functional mapping-guided surgery was performed using electrophysiological brain mapping techniques, namely intraoperative neuromonitoring (IONM) with or without awake craniotomy (AC). The primary outcome was the rate of postoperative neurological deficits. The secondary outcomes were the extent of resection, the rate of surgical complications, the Engel Outcome Scale score, and the progression-free survival (PFS) rate.

RESULTS: Twenty-eight patients were included (43% males), with a mean age of 37.5 years. Their median preoperative Karnofsky Performance Scale score was 90. The predominant histopathology was astrocytoma (n = 20, 71%), and the primary site was peritumoral in 19 patients (68%). Seizures were the most common presenting symptom (71%). Resection was performed using either IONM alone (39%) or combined with AC (61%). Gross total resection was achieved in 20 patients. Six patients (21%) developed postoperative complications. Patients were followed up for a mean of 39.9 months. At discharge, 12 patients (43%) had experienced new or worsened neurological deficits, but nine of them later showed significant improvement. Sixteen patients achieved Engel class 1 seizure control, and the median PFS was 34 months. Two patients died during the study period.

CONCLUSION: This study demonstrates that our institution's protocol for integrating functional mapping into the surgical management of DLGGs achieves a solid onco-functional balance.

KEYWORDS: Awake surgery, Brain mapping, Direct electrical stimulation, Extent of resection, Low-grade glioma, Neuro-oncology

AC: Awake craniotomy, **CI:** Confidence interval, **CMAPs:** Compound muscle action potentials, **CNS:** Central nervous system, **DLGGs:** Diffuse low-grade gliomas, **DWI:** Diffusion-weighted imaging, **EOR:** Extent of tumoral resection, **GTR:** Gross total resection, **IDH:** Isocitrate dehydrogenase, **IONM:** Intraoperative neurophysiological monitoring, **KPS:** Karnofsky Performance Scale, **LGGs:** Low-grade gliomas, **LMICs:** Low- and middle-income countries, **MEP:** Motor-evoked potential, **MRI:** Magnetic resonance imaging, **MRC:** Medical Research Council, **NF:** Neurofibromatosis, **NIHSS:** National Institutes of Health Stroke Scale, **nTMS:** Navigated transcranial magnetic stimulation, **PET:** Positron emission tomography, **PFS:** Progression-free survival, **PMC:** Premotor cortex, **PMR:** Piecemeal resection, **PR:** Partial resection, **rCBV:** Relative CBV, **RR:** Risk ratio, **RS-fMRI:** Functional MRI of the resting state, **RTNT:** Real-time neuropsychological testing, **SBB:** Stereotactic brain biopsy, **SD:** Standard deviation, **SEPs:** Somatosensory-evoked potentials, **SGR:** Sulcus-guided resection, **SLF:** Superior longitudinal fasciculus, **SMA:** Supplementary motor cortex, **STR:** Subtotal resection, **STROBE:** Strengthening the Reporting of Observational Studies in Epidemiology, **TES:** Transcranial electrical stimulation, **VTE:** Venous thromboembolism, **WHO:** World Health Organization

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■ INTRODUCTION

Each year, around 330,000 individuals globally are diagnosed with a brain tumor, and another 227,000 are estimated to die from brain tumors (17). Low-grade gliomas (LGGs) account for approximately 25% of primary tumors of the central nervous system (CNS; 31); they represent a heterogeneous group of neuroepithelial tumors arising from glial cells in the CNS (5). Historically, diffuse LGGs were classified as grade 2 according to the World Health Organization's (WHO) criteria of histopathological features. However, the latest WHO classification, published in 2021, incorporates recent advances in molecular genetics to enable a more integrated diagnosis (48). One of the most important molecular findings is the isocitrate dehydrogenase (IDH) enzyme mutation status. The high prevalence of IDH mutation in the glioma cells of WHO grade 2 and 3 tumors suggests that such mutation is a driver in tumorigenesis (4).

Diffuse low-grade gliomas (DLGGs) occur particularly frequently in males aged 40–50 years. Evidence-based risk factors include ionizing radiation and inherited tumor syndromes (9). The clinical effects are highly variable, with survival ranging between 2 and 15 years. Almost 10% of DLGGs are incidentally discovered, and when symptomatic, between 70% and 90% of patients present with seizures (41).

Treatment strategies have long been controversial due to the slow-growing and diffusely infiltrative nature of DLGGs. Although the tumors are classified as low-grade, a recent paradigm shift based on evidence supports the active treatment of DLGGs, instead of watchful waiting, to improve the survival outcomes and reduce the rate of epilepsy (7,8,22,44). Several studies have also advocated an active strategy for incidentally discovered DLGGs (13). The most recent treatment approach is partly driven by epidemiological studies that have documented a 10–40% rate of malignant progression and an average growth velocity of 6 mm/year (27,33). The oncological goal of treatment is now well established. The maximum extent of resection (EOR) required to achieve gross total resection (GTR) is the most significant predictor of both overall survival and progression-free survival (PFS). The role of adjuvant chemoradiotherapy has been questioned, with some authors arguing that early chemoradiotherapy may lead to tumor dedifferentiation (32).

Functional outcomes after glioma surgery in eloquent areas remain a topic of debate. Eloquent areas are defined as regions of the brain with readily identifiable neurological functions, in which injury or perilesional edema disrupt network dynamics, leading to neurological consequences and resultant disability (20). Neurosurgeons face considerable difficulties in balancing the EOR of diffuse infiltrative gliomas against the functional deficits associated with aggressive resection (12,35,39). Advanced imaging techniques, neuro-navigation, intraoperative neurophysiological monitoring (IONM), and awake craniotomy (AC) are valuable tools in the neurosurgical arsenal to achieve onco-functional balance. These techniques are crucial, despite the logistical barriers that may be present in low- and middle-income countries (LMICs; 19).

Our group has prepared a retrospective cohort study of our experience in implementing functional mapping-guided resection of supratentorial adult-type diffuse low-grade gliomas (DLGGs). This is a growing practice in low-middle income countries (LMICs) despite logistical barriers. To our knowledge, this cohort study, which was reported according to STROBE guidelines, is the first report on the use of functional mapping-guided resection of DLGGs in Ain Shams University.

■ MATERIAL and METHODS

This retrospective single-arm observational study analyzed prospectively collected patient data at Ain Shams University Hospitals in Cairo, Egypt, from January 2016 until August 2024. Patient data were anonymized to maintain the patients' privacy. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. Our ethically compliant study protocol was submitted for approval by the Institutional Review Board Ethics Committee [FMASU MS124/2024]. The results are reported in compliance with the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE; 51).

We performed a retrospective chart review of patients who underwent surgical resection of radiologically suspected DLGGs based on magnetic resonance imaging (MRI) criteria (49). The inclusion criteria were as follows: 1) adult patients aged 18 years or older; 2) Karnofsky Performance Scale (KPS) scores between 60% and 100%; 3) tumor located in or near (within 15 mm of) supratentorial eloquent brain areas, as identified by clinical assessment coupled with imaging techniques (20); and 4) surgical treatment using electrophysiological brain mapping in the form of IONM with or without AC.

The exclusion criteria were as follows: 1) patients presenting with recurrent tumors; 2) severe preoperative neurologic deficits (motor power below grade 3, severe dysphasia); and 3) histopathological diagnoses other than adult-type DLGGs according to the WHO criteria.

The aim of our study was to determine the feasibility of performing resection guided by intraoperative functional mapping for reducing the rate of postoperative neurological deficits in the DLGG patient population. Functional mapping-guided resection using intraoperative visualization tools and monitoring is the safest approach to surgical resection of DLGGs (identified as signal abnormality on MRI T2/FLAIR sequences). The relevant tools include neuro-navigation systems and/or intraoperative ultrasound, and monitoring techniques include electrophysiological brain mapping methods with or without AC.

Preoperative Assessment

Clinical

In the week preceding surgery, a full neurological evaluation, including a seizure assessment and performance status assessment using the KPS, was conducted. Dominant upper-limb laterality was determined using the Edinburgh Handedness Inventory (29).

Radiological

At our center, patients are provisionally diagnosed with DLGGs using preoperative contrast-enhanced brain MRI. Pre-surgery MRI exams are updated to ensure an interval of no longer than 30 days between the examination and the surgery. Functional MRI and diffusion tensor imaging tractography are routinely used in our institution for tumors located in eloquent areas. Magnetic resonance spectroscopy is reserved for selected cases with a high degree of uncertainty.

Surgical Procedures

Our protocol for AC is similar to that published by Albuquerque et al. (3). We perform routine preoperative neuropsychological evaluations to assess the feasibility of the procedure. Patients are extensively educated about the surgical stages and are shown pictures and words that will be used later (during intraoperative language mapping) to tailor the intraoperative testing. The patient's position is adjusted for maximum comfort, after which general anesthesia is administered using propofol and dexmedetomidine. Volatile anesthetics are avoided because they interfere with evoked potentials.

A scalp block is performed on the surgical side through seven main nerves: supratrochlear, supraorbital, zygomaticotemporal, auriculotemporal, auricular major, occipital minor, and occipital major. Then, local anesthesia is applied to the three points of the skull fixator. The craniotomy procedure is conducted under general anesthesia, with neuro-navigation used to plan the incisions and bone flaps. Once the tumor area is exposed, the patient is gradually weaned off the general anesthesia until they are fully awake and cooperative.

Cortical mapping is performed using an Ojemann Cortical Stimulator device equipped with a bipolar stimulation probe, which has a 5-mm distance between the tips. The device is configured to apply a negative biphasic wave, a fixed pulse frequency of 60 Hz, and a pulse phase duration of 1 ms, with the stimulus beginning at an amplitude of 1.5 mA. When the central lobe is mapped, the amplitude intensity is adjusted to the lowest value that generates speech arrest or a positive motor response. During this process, the patient performs a dual task of counting—which involves automatic language—and rhythmically contracting the contralateral upper limb.

When other cortical regions are mapped, the lowest value that elicits a functional response is utilized. If 1.5 mA causes an immediate response, the amplitude is reduced to 1.0 mA to determine the lowest intensity that produces functional findings. A region is considered functional when it exhibits neurological alterations in three non-consecutive stimulations. An amplitude above 5 mA and a stimulus duration longer than 4 s are avoided to prevent seizures during the procedure. In the event of a seizure crisis, cold lactated Ringer's solution is used to control it.

Tumor resection is alternated with subcortical stimulation, during which time continuous cognitive assessment is conducted. Tissue resection continues until the functional limits are defined at both the cortical and subcortical levels. An ultrasonic aspirator is used if relatively hard tumors are present.

Afterward, the patient is administered light sedation with low doses of remifentanyl and propofol until the procedure is complete.

As described by Obermueller et al., we routinely utilize continuous IONM through motor-evoked potential (MEP) monitoring using a strip electrode that has four to eight contacts (28). To confirm the locations of the pre- and post-central gyri and the central sulcus, we employ somatosensory evoked-potential phase reversal. For the detection of compound muscle action potentials (CMAPs), 27-gauge disposable subdermal needle electrodes are placed in a bipolar configuration, approximately 10 mm apart, over the relevant muscles on the contralateral side of the tumor. The stimulation parameters we use are square-wave pulses with a duration between 200 μ s and 300 μ s, a frequency of 350 Hz, and a train of five pulses.

We begin the stimulation at 6 mA and continuously increase the intensity in steps of 1 mA, either until we are able to record a CMAP or until an upper limit of 30 mA is reached without eliciting a CMAP. Every minute, sequential MEP monitoring is performed using anodal direct cortical or subcortical stimulation of the Rolandic cortex or corticospinal tract, until the end of resection and before dural closure. The obtained data are processed by the neuromonitoring system. MEPs are continuously recorded and analyzed in real time, and their amplitude and latency are monitored by a neurophysiologist. Depending on the status of the resection, intervals are shortened during critical steps to ensure maximum safety.

During resection, a decrease in amplitude of 50% or more below the baseline is considered a significant decline and is immediately reported to the surgeon. The surgeon may then consider reversing the underlying surgical step, removing spatulas, or irrigating the exposed cortex and vasculature with warm Ringer's solution. Moreover, when the resection is close to major blood vessels, irrigation with papaverine is performed to potentially reverse or avoid vasospasm. As soon as the MEP amplitudes stabilize or recover, tumor resection continues. If MEP fails to recover, resection is halted at this part of the resection cavity.

Follow-Up

Early postoperative phase

Our institution's protocol after surgery includes an early postoperative neurological examination to detect signs of neuro-worsening (e.g., consciousness level, motor power, and speech). A computed tomography scan is also performed within 4 h postoperatively to exclude early surgical complications, such as intracranial hemorrhage or significant brain edema.

Late postoperative phase

We conduct regular clinical and radiological follow-ups (MRI brain with contrast) every three months for two years, and then every six months thereafter. Further adjuvant therapeutic interventions, if any, such as radiotherapy and/or chemotherapy for selected cases with residual tumors, or redo surgery for recurrent cases, are documented.

Data Collection

Data were collected prospectively during the preoperative period (at the time of diagnosis and immediately before surgery) and again in the intraoperative period, as well as in the postoperative period immediately after surgery and in long-term follow-up. We recorded demographic, clinical, radiological, histopathological, surgical, and adjuvant treatment variables.

The primary outcomes were the rates of postoperative neurological deficits and postoperative KPS scores. Postoperatively, new deficits were considered severe if they involved any of the following: muscle strength graded 1 to 3 on the Medical Research Council (MRC) scale, hemianopia, severe dysphasia or aphasia, or a vegetative state. All other neurologic deficits were considered mild to moderate, including grade 4 paresis, isolated central facial palsy or other cranial nerve deficits, dysnomia, somatosensory syndrome, and parietal syndrome. We defined transient deficits as those that resolved completely within three months after surgery and permanent deficits as those that persisted beyond three months (14). To obtain objective assessments, we used the MRC scale to evaluate motor strength (23), the National Institutes of Health Stroke Scale (NIHSS) sensory subtest for sensation (11), the modified Aachen Aphasia Test for speech (43), and perimetry for the visual field (if a field defect was clinically suspected based on the confrontation test).

The secondary outcomes were the EOR, the rate of surgical complications, the Engel Outcome Scale score for seizure outcomes at the last follow-up (at least 1 year postoperatively), and PFS rates. EOR was classified as gross total resection (GTR), subtotal resection (STR), or partial resection (PR). GTR was defined as 90% or more resection of the preoperative T2 or FLAIR signal abnormality; STR was between 70% and 89% resection; and PR was less than 70% resection (21).

Statistical Analysis

Data were tabulated and analyzed using the Statistical Package for Social Sciences (SPSS, version 25.0, Chicago, IL, USA). Quantitative variables having a normal distribution (e.g., age) were reported as the mean $\pm$ standard deviation. Non-normally distributed data were expressed as the median along with interquartile ranges. Quantitative parametric variables (e.g., KPS scores) were compared using Student's t-test and analysis of variance. For quantitative variables suited to nonparametric analysis, the Mann-Whitney and Kruskal-Wallis U tests were employed. Qualitative data on the categorical variables were expressed as an absolute number (n) and a relative frequency (%). Comparisons between the groups were assessed by chi-squared (χ^2) tests. The MedCalc 18.11 program was used to calculate the RR and the 95% CI. Correlations were assessed using Spearman's rank tests. Kaplan-Meier curves were used to evaluate the PFS among the study group. All statistical comparisons were two-sided and were considered significant at $p < 0.05$.

RESULTS

Patient Demographics and Clinical Characteristics

The chart review identified 28 patients who were eligible to be included in our study. The cohort consisted of 12 males

and 16 females, with a mean age of 37.5 years (range 22–58 years). Only one patient was left-handed, with right-sided hemispheric dominance. The median preoperative KPS score was 90 (Table I).

Tumor Characteristics

Across all patients, the median tumor diameter was 49.2 mm. The predominant histopathology was astrocytoma (n=20, 71.4%), and more than half of tumors had an unknown IDH status (57.1%). Most patients (n=19, 67.9%) had peritumoral tumors, with the second most frequent location being the frontotemporal area (n=8, 28.6%). Seizures were the most common presenting symptom (n=20, 71.4%). Four patients had an incidental DLGG, discovered during work-up for a mild headache (Table II).

Treatment Details

Resection guided by functional mapping was utilized for all patients, using either IONM alone (39.3%) or combined with AC (60.7%). GTR was achieved in 20 patients (71.4%). Five patients (17.9%) had an STR because the tumor boundaries overlapped with critical functional regions. Only two patients (7.1%) developed intraoperative seizures, which were aborted by cold Ringer's solution irrigation. The occurrence of seizures did not prevent the completion of the procedure in either patient.

The procedure was aborted for only one patient in the entire group, with a biopsy alone being performed; the reason was extensive tumor encroachment on the motor functional tracts.

Table I: Baseline patient characteristics (n = 28)

Characteristic	Value
Age at surgery (years)	
Mean $\pm$ SD	37.5 $\pm$ 10.5
Median (IQR)	36 (30-44)
Gender, male n (%)	12 (42.9)
Hand laterality, n (%)	
Right	27 (96.4)
Left	1 (3.6)
Preoperative KPS, n (%)	
Mean $\pm$ SD	89 $\pm$ 9
Median (range)	90 (70-100)
Comorbidities, n (%)	
Diabetes mellitus	2 (7.1)
Hypertension	1 (3.6)
Kidney disease	1 (3.6)
Cardiac disease	0
Liver disease	0

IQR: Interquartile range, **KPS:** Karnofsky performance scale, **SD:** Standard deviation

Table II: Tumor histopathology and clinical features.

Characteristic	Value
Median preoperative tumor largest diameter on T2-weighted MRI in mm (range)	49.2 (17.3-127.3)
Histopathology, n (%)	
Astrocytoma	20 (71.4)
Oligodendroglioma	8 (28.6)
IDH-mutant status, n (%)	
Mutant	12 (42.9)
Wild	0 (0)
Unknown	16 (57.1)
Tumor laterality, n (%)	
Right	12 (42.9)
Left	16 (57.1)
Tumor site, n (%)	
Central lobe	19 (67.9)
Temporal lobe	3 (10.7)
Frontotemporal	3 (10.7)
Frontal lobe	2 (7.1)
Insula	1 (3.6)
Presenting symptom, n (%)	
Seizure	20 (71.4)
Headache	4 (14.3)
Focal neurologic deficit	3 (10.7)
Seizure & focal neurologic deficit	1 (3.6)
Behavioral changes	0 (0)

IDH: Isocitrate dehydrogenase, **MRI:** Magnetic resonance imaging

Postoperatively, six patients (21.4%) developed complications related to the surgery. Three patients developed tumor-bed hemorrhages that were managed conservatively. Postoperative leaking of cerebrospinal fluid or pseudomeningocele occurred in two patients and was successfully managed by lumbar drain insertion for five days. A deep incisional surgical-site infection occurred in one patient and required multiple debridement procedures, followed by a local scalp flap reconstruction performed by our plastic surgery team. Adjuvant treatment was utilized in 13 patients (46.4%; Table III).

Functional and Oncological Outcomes

Postoperative neurological function was assessed at discharge and during follow-up visits, as described in the previous section. Patients were followed up for a mean of 39.9 months (3.32 years). At discharge, 12 patients (42.9%) experienced new or worsened neurological deficits. However, by the three-month follow-up, nine of them showed significant im-

Table III: Treatment details and complications

Characteristic	Value
Surgical therapy, n (%)	
IONM only	11 (39.3)
AC with IONM	17 (60.7)
Extent of resection, n (%)	
GTR	20 (71.4)
STR	5 (17.9)
PR	2 (7.1)
Biopsy	1 (3.6)
Intraoperative complications, n (%)	
None	25 (89.3)
Seizures	2 (7.1)
Procedure aborted	1 (3.6)
Initial adjuvant therapy, n (%)	
None	15 (53.6)
Radiotherapy	7 (25.0)
Chemoradiation	5 (17.9)
Chemotherapy	1 (3.6)
Redo surgery	0 (0)
Postoperative complications (within 30 days) ^a , n (%)	
None	22 (78.6)
ICH	3 (10.7)
CSF leak / Pseudomeningocele	2 (7.1)
SSI	1 (3.6)
VTE	1 (3.6)

AC: Awake craniotomy, **CSF:** Cerebrospinal fluid, **GTR:** Gross-total resection, **ICH:** Intracerebral hemorrhage, **IONM:** Intraoperative neuromonitoring, **PR:** Partial resection, **SSI:** Surgical site infection, **STR:** Subtotal resection, **VTE:** Venous thromboembolism

^a Complications are not mutually exclusive. Some patients developed > 1 complication.

provement; the remaining three (10.7%) had persistent mild to moderate deficits and were referred to rehabilitation therapy.

Notably, none of the patients experienced severe postoperative neurological deficits, and most patients (89.3%) maintained or improved their preoperative neurological status. The median postoperative KPS was 90, with an interquartile range of 80 to 100. There was no significant difference between pre- and postoperative KPS, with a mean difference of 6.42 points (95% CI=-4.49 to 17.35, p=0.238). Around 64% of patients had a similar or improved postoperative KPS (n=18). Postoperative Engel class data were available for only 25 patients, as three patients had follow-up lasting less than a year (Table

Table IV: Functional and oncologic outcomes

Characteristic	Value
Follow-up (months)	
Mean±SD	39.9±24.4
Median (IQR)	38.5 (19.5-60)
Postoperative KPS	
Mean±SD	82±28
Median (range)	90 (0-100)
New neurologic deficit (n=12), n (%)	
Early	9 (32.1)
Late	3 (10.7)
Severity of neurologic deficit (n=12), n (%)	
Mild-moderate	12 (100)
Severe	0 (0)
Engel Class (n=25), n (%)	
1	16 (64)
2	6 (24)
3	2 (8)
4	1 (4)
Recurrence/Progression	7 (25)
PFS (months)	
Mean±SD	36.0±21.5
Median (IQR)	34 (18-54)
Salvage treatment (n=7), n (%)	
Radiotherapy	3 (42.9)
Chemoradiotherapy	2 (28.6)
Stereotactic biopsy	1 (14.3)
Re-excision followed by chemoradiotherapy	1 (14.3)

IQR: Interquartile range, **KPS:** Karnofsky performance scale, **PFS:** Progression-free survival, **SD:** Standard deviation

IV). There was no statistically significant correlation between the EOR and Engel class (Spearman's rho = 0.298, p = 0.148; Figure 1).

By the end of the follow-up period, 21 patients (75%) remained progression-free. Among the seven patients (25%) who experienced tumor recurrence or progression, four had undergone non-GTR. During a median follow-up period of 38.5 months (ranging from 3 to 97 months), the median PFS was 34 months (range: 3 to 75 months; Figures 2 and 3). PFS was significantly longer in patients who underwent GTR than those who received STR (p<0.05; Figures 4,5). There was no significant difference in the PFS rates for IONM versus IONM with AC (log rank = 0.028, p=0.866).

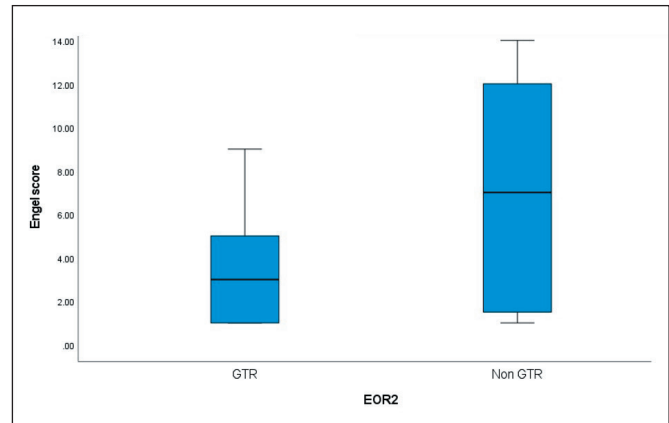


Figure 1: Box plot of Engel outcome scale with extent of resection. Test of significance: Mann-Whitney, p = 0.146.

Two patients died during our study period. One of them had undergone a biopsy and had a follow-up of 42 months, with a PFS of 34 months. The other patient underwent STR and had a follow-up of 82 months, with a PFS of 65 months. At the time of writing, another patient had recently been admitted to the intensive care unit, 24 months after an STR. Her PFS was 17 months, and she was receiving chemoradiotherapy for malignant progression documented by magnetic imaging spectroscopy. We conducted a statistical analysis to identify predictors of the occurrence of new or worsened neurologic deficits after surgical resection. None of the examined variables had a statistically significant relation to new neurologic deficits (Table V).

DISCUSSION

Patients with DLGGs are a challenging population for neurosurgeons, despite recent advances in imaging and intra-operative adjuncts. The main reason is the slow infiltration of these tumors, which causes deafferentation of the cortico-subcortical local and distant networks. The challenges are accentuated in the resource-limited settings of most LMICs. For example, a recently published review of DLGG literature in Africa highlighted a knowledge gap and a lag in the uptake of evidence-based techniques for glioma surgery (30). In this paper, we report our LMIC institution's experience with functional mapping-guided resection in 28 cases of eloquent area DLGGs. The resection involved either IONM alone (39% of patients) or combined with AC (61%).

In general, most patients with DLGGs are young adults with good health and functional status, who often present with seizures and a tumor in the perirolandic area; these tumors typically have a volume between 40 cm³ and 50 cm³. The same trends were evident in our study. Our patients had a mean age of 37.5 years, a median preoperative KPS of 90, a seizure rate of 71.4%, and a median tumor diameter of 49.2 mm. There was central lobe involvement in 70% of the patients. The demographic data were similar to other previously published large cohorts, although there was a slight female predominance in our series, possibly due to the small sample (21,24).

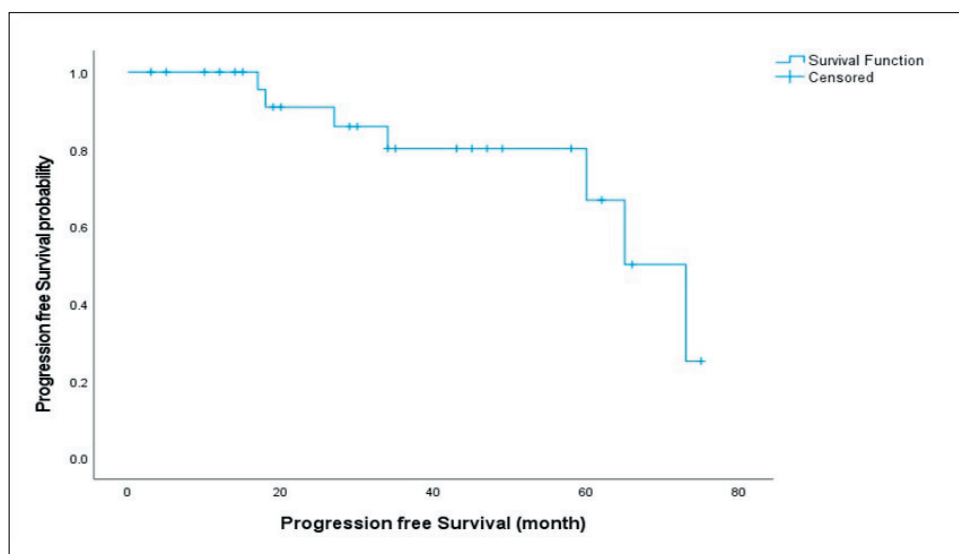


Figure 2: Kaplan-Meier curve for progression-free survival of the entire cohort (n=28).

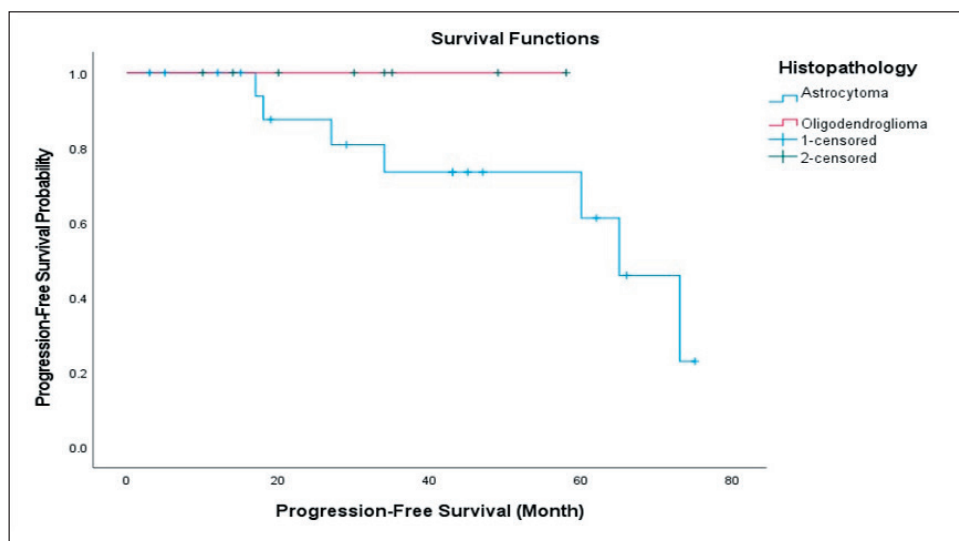


Figure 3: Kaplan-Meier curve for progression-free survival stratified by histopathology.

Our GTR rate (defined as $\geq 90\%$ resection) was 71.4%. Rates reported in the literature differ according to the definitions used and range from 50% to 80% (2). Intraoperative neurophysiology provides neurosurgeons with real-time assessments of functionality, which allows for maximum resection with minimal safety concerns.

In terms of functional outcomes, approximately 43% of our patients developed new or worsened neurological deficits, of which only 11% persisted beyond three months in the form of mild to moderate deficits. Compared to historical cohorts without IONM, the rate of permanent severe deficits was reduced by more than half through the use of IONM (15). Our results are comparable to those in other studies utilizing function-guided resection, in which the rate of new deficits ranged from 20% to 45% and the rate of permanent deficits ranged from 5% to 10% (10,21,24). The slightly high rate of observed deficits in our sample may be attributable to the neurophysiology protocol our organisation follows, which is still a matter of debate (34,46).

Finally, we analyzed factors that may predict new neurological deficits. The results were consistent with the literature, namely, GTR is not associated with worse functional outcomes, and peritumoral gliomas have comparable outcomes to gliomas in other areas (16,45). However, our results were not statistically robust because the sample was too small. The use of AC has elsewhere been shown to lower the risk of long-term neurological and language deficits, while achieving a greater extent of tumor resection and shorter hospital stays (40).

In terms of seizure outcomes, Engel class 1 was found in 64% of our patients. The results indicated a statistically non-significant trend of improved Engel scores associated with more extensive EOR. The literature is similarly conclusive that greater resection improves seizure outcomes, with the rate of freedom-from-seizure ranging from 60% to 80% (44,52,54). Xu et al. retrospectively analyzed 128 DLGG patients who presented with seizures to determine the optimal EOR threshold to achieve seizure freedom. They found a seizure-freedom rate of 82%, and their analysis revealed that a higher EOR

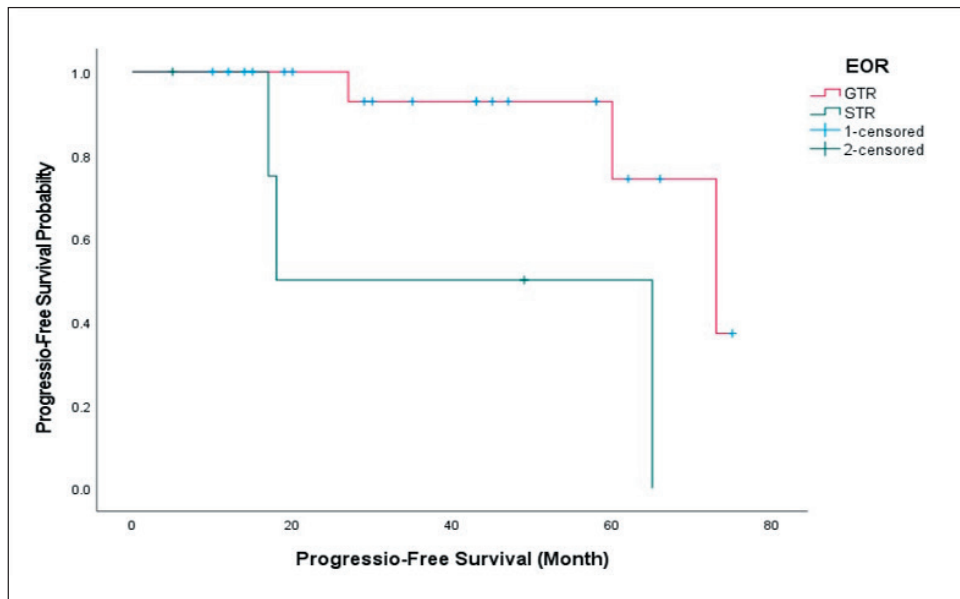


Figure 4: Kaplan-Meier curve for progression-free survival stratified by extent of resection (GTR vs. STR). Mantel-Cox log rank = 6.05 ($p = 0.014$).

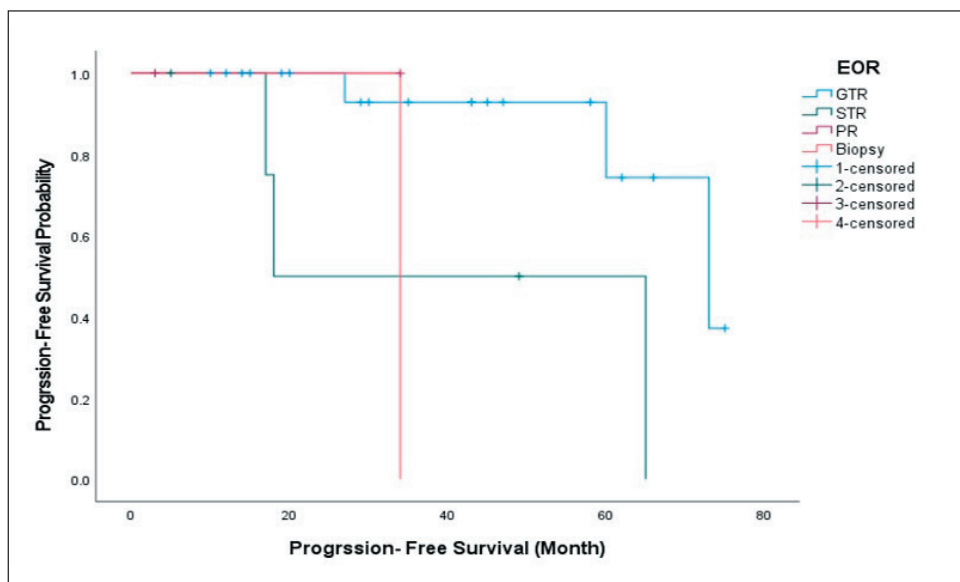


Figure 5: Kaplan-Meier curve for progression-free survival stratified by extent of resection.

increased the odds of seizure freedom up to 11-fold, with a minimum threshold of 80% resection (52).

Typically, up to 50% of DLGGs may recur within five years of resection. The median follow-up duration in our study was 38.5 months, just a little more than three years. Hence, some recurrence or progression events may have been under-detected. We observed a 25% recurrence/progression rate, with a median PFS of 34 months. None of the cases of oligodendroglioma recurred or progressed during our series. This can be explained by the favorable baseline prognosis of oligodendroglioma compared to astrocytoma. This point highlights the need for prolonged follow-up when studying these subgroups to ensure that sufficient progression events are covered and accurately identify the benefits of aggressive surgery (42,47). Despite our small sample and low incidence of events in the

first three years, the results indicate that GTR significantly prolonged PFS, compared to the results after STR.

Another factor to consider is the role of adjuvant treatment. Just under half of the patients in our series received adjuvant radiotherapy and/or chemotherapy. A recent systematic review of 29 studies highlighted their role in prolonging overall survival and PFS (8). There is ongoing debate regarding the definition of “high-risk” criteria that determine the need for adjuvant treatment, including the patient’s age, the tumor size, EOR, and molecular signatures (9,18). The role of adjuvant treatment as a potential modifier of the effect of surgery needs further exploration.

The future of functional mapping-guided glioma surgery is still developing. The debate about whether maximal resection improves the outcomes is currently focused on supratotal resec-

Table V: Statistical analyses of predictors of new neurologic deficits

Characteristic	Negative (No deficit)	Positive (New deficit)	RR (95% CI)
Age (years)			
≤ 38*	11	7	1.29 (0.55-3.00)
> 38	5	5	
Gender			
Female*	9	7	0.95 (0.40-2.03)
Male	7	5	
Tumor site			
Central	9	10	2.37 (0.65-8.64)
Other*	7	2	
Histopathology			
Oligodendroglioma*	4	4	0.80 (0.33-1.92)
Astrocytoma	12	8	
Presenting symptom			
Seizure	13	7	0.56 (0.22-1.25)
Other*	3	5	
Preoperative KPS			
< 100*	13	9	1.22 (0.48-3.14)
100	3	3	
Surgical therapy			
IONM*	4	7	0.46 (0.20-1.09)
IONM + AC	12	5	
EOR			
Non-GTR*	5	3	1.20 (0.43-3.14)
GTR	11	9	
Adjuvant treatment			
No*	8	7	0.82 (0.34-1.98)
Yes	8	5	

AC: Awake craniotomy, **CI:** Confidence interval, **EOR:** Extent of resection, **GTR:** Gross-total resection, **IONM:** Intraoperative neuromonitoring, **RR:** Risk ratio

* Reference group

tion beyond the tumor borders that are detectable on FLAIR imaging. This approach is made possible by the slow growth of the tumor, allowing for cortical adaptor mechanisms that enable the functional and morphologic reorganization of brain circuits (25,37). Adjuncts that may increase the EOR have been shown to improve the outcomes. A prominent example is intraoperative MRI, which was reported to alter surgical decision-making and led to additional tumor resection in up to 60% of cases (53). Advances in IONM and neurophysiological warning signs have led to the prospect of using direct cortical stimulation combined with transcranial electrical stimulation

(TES) for monitoring motor-evoked potentials. This method has the theoretical benefit of increasing the specificity (i.e., reducing false-negative results) due to the poor stimulation focality of TES (50).

Rammeloo et al. recently called for the development of a novel preoperative classification system to assess eloquence, given the notable variation in current definitions and assessment methods. This point is particularly relevant given the shift from a localizationist view to a perspective that is more related to connectivity and connectomics. The authors proposed that eloquence should not be used as a preoperative factor in personalized medicine models, as it might lead to suboptimal treatment for subgroups of glioma patients (36).

To our knowledge, ours is the first report about functional mapping-guided resection of DLGGs in Egypt, although an earlier study of 20 patients described the use of navigation-guided resection of DLGGs (1). The success of functional mapping-guided resection in our study highlights the feasibility of applying advanced neurosurgical techniques in LMIC settings where resources are limited. Our results are consistent with similar studies in other LMICs, namely a GTR rate of 71%, a post-operative complication rate of 21%, and favorable functional outcomes (32% early deficits and 11% late deficits). Other reported GTR rates, complication rates, early deficits, and late deficits range between 40% and 80%, 10% and 20%, 10% and 30%, and 5% and 15%, respectively (3,6,26,38). While LMICs often face barriers such as the high cost of advanced technologies and a lack of specialized personnel, targeted investments in affordable alternatives and training have yielded positive outcomes. For instance, Abdullah et al. demonstrated that low-cost neuro-navigation systems improved the precision of glioma surgeries, resulting in outcomes similar to those achieved in high-income settings (1).

To address the ongoing disparity in glioma care between high-income countries and LMICs, future research should focus on validating low-cost intraoperative technologies and developing neurosurgical training programs tailored to the unique challenges of LMICs. Such research would enable doctors in LMICs to enhance their surgical precision, as well as improving the survival rates among glioma patients and reducing the incidence of postoperative deficits. Additionally, global collaboration between neurosurgeons in both LMICs and in high-income countries could further bridge the gap in access to advanced surgical techniques. In the future, research reports from other institutions in Egypt and Africa would be helpful for refining the protocols for safe and effective glioma surgery in resource-limited settings.

Limitations

Our study had several limitations. First, the observational retrospective methodology may have introduced potentially unknown sources of bias. Second, seizure semiology was not recorded in our database. Third, the small sample and lack of a control group limited the power of our investigation to strongly identify the effect of neuromonitoring on functional outcomes. Fourth, the lack of routine molecular diagnosis at our center led to an overreliance on tumor diagnosis using histopathological criteria, contrary to WHO recommendations.

Similarly, the determination of EOR was based on subjective interpretation by a radiologist and not volumetric measurements, which could have introduced variability and reduce precision. In addition, we did not categorize patients with GTR into complete (100%) and near-total ($\geq 90\%$) resection of tumor. The intended EOR prior to neuromonitoring use was not recorded, which meant the effect of IONM on the final EOR could not be determined. Finally, the study period spanned eight years. During that period, several updates to adjuvant treatment protocols were implemented, which could have had significant modifier effects on the PFS rates.

CONCLUSION

The results of this study indicate that functional mapping-guided resection of DLGGs in eloquent brain areas allows for maximal tumor removal, while preserving neurological function. This approach therefore achieves onco-functional balance. GTR was associated with optimal oncological outcomes and the best possible PFS, with minimal impact on the patients' postoperative quality of life. Most of the postoperative neurological deficits observed in our sample were transient. Overall, the findings support the integration of functional mapping into the surgical management of DLGGs in hospitals in LMICs.

Declarations

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Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Disclosure: The authors declare that there are no conflicts of interest related to this study.

AUTHORSHIP CONTRIBUTION

Study conception and design: STE-S, AGA-A

Data collection: STE-S

Analysis and interpretation of results: AMA, MMA

Draft manuscript preparation: STE-S

Critical revision of the article: AMA, MMA, AGA-A

Other (study supervision, fundings, materials, etc.): AGA-A

All authors (STE-S, AMA, MMA, AGA-A) reviewed the results and approved the final version of the manuscript.

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