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Towards a sensitive awake craniotomy: assessment of electrical mapping thresholds

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ABSTRACT

Background. Awake surgery is currently a safe and reliable alternative for identifying and preserving functional areas. However, this protocol has evolved over time to minimize the occurrence of electrical stimulation-induced seizures and postoperative deficits.
Objective. The aim of this study is to highlight both internal and external factors influencing the language and sensorimotor thresholds of electrical stimulation mapping (ESM) during gliomas awake surgery.
Material and methods. From October 2016 to April 2022, we performed a retrospective study on 74 patients underwent awake craniotomy of gliomas in two series based on ESM: group 1 and group 2. Preoperatively and three months after surgery, general performance and neurological deficits were assessed according to the type, location, and side of the tumor in correlation with ASA, BMI, Mallampati and KPS indexes.
Results. The outcome shows that the median patient age was 49 years old in a range of [13-70], functional mapping was performed in language areas for 96% of patients and motor functions for 54%. In addition, 55.5% of the patients had HGG, 40.5% had LGG, and 4% had AVMs. Most lesions were in the temporal area (40.5%), followed by the frontal area (31%), 24.5% for insular area, 4% for the parietal area, and 85% of patients had left-sided lesions. The overall rate of intraoperative complications fell from 16.2% in group 2 to 1.35% in group 1.
Conclusions. Under the ESM threshold of group 1, a high-quality of awake surgery can be used with optimally low complications and failure rates regardless of BMI, ASA rating, Mallampati and KPS scores or smoking status.

Keywords: awake craniotomy, glioma, electrical stimulation mapping, functional brain mapping

Abbreviations

AVMs – Arterio-venous malformations.
ASA – American Society of Anesthesiologists
BMI – Body mass index
CSF – Cerebro-spinal fluid.
DES – Direct electrical stimulation.
ECoG – Electrocorticography
EOR – Extent of resection
EMS – Electrical mapping stimulation
FBM – Functional brain mapping.
FRT – Functional recovery time.
HGG – High grade glioma.
LGG – Low grade glioma.
LMA – Laryngeal mask airway
KPS - Karnofsky performance scale
SD - Standard deviation.
STIsm - Stimulation threshold intensity for sensorimotor function.

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INTRODUCTION

The combination of awake craniotomy and new techniques like neuronavigation is still the best method for resection with a high extent of resection (EOR), improving overall survival, progression-free survival, and malignant transformation, especially in low-grade gliomas based on functional limits to find and perform detailed mapping to protect functional areas during cortical or eloquent resection [1,2,3,4,5].

Since Horsley's initial description of awake surgery, there has been a lack of standardization due to the various techniques and methodologies described in the literature for mapping functional sites [6,7]. This may be attributable to the complexity of the procedure, the patient recruitment requirements, the occurrence of intraoperative stimulation-induced seizures, and failure rates ranging from 2.3% to 6.4%, according to previous studies demonstrating the value of cortical and subcortical mapping for glioma resections, as well as the significance of resection extent for both high- and low-grade gliomas [1,8,9,10,11,12-13]. Indeed, this lack, affecting the sensitivity of the functional mapping, constitutes a boundary limit. So, optimization under electrical threshold conditions remains a necessity to improve the functional mapping quality. This study aims to share our experience in determining optimal thresholds to maximize functional mapping and defining factors that favor the risk of failure during awake craniotomies.

MATERIALS AND METHODS

Patient selection and inclusion criteria

We studied retrospectively 74 patients undergoing awake craniotomy performed by the same neurosurgical team between 2016 and 2022 for the resection of brain tumors in functional areas. On preoperative MRI, patients were included in the study if they had intra-axial and supratentorial lesions in or adjacent to regions thought to have language or sensorimotor function.

Recruitment of appropriate clinical cases requires exclusion of contraindications such as meningeal tumors, brainstem tumors, and metastases. We have started with a careful patient selection, with the first patients being systematically adult patients, with left hemisphere LGG. Progressively, we have extended our indications for awake procedures for right hemisphere LGG, for some carefully selected HGG (and one of the important concerns in our context is the Karnovsky score being high enough so that the patient can really benefit from the surgery), and some cases of AVMs [14,15]. Furthermore, patients who passed sensorimotor and linguistic mapping allowed us to determine the sensorimotor current threshold. After reviewing intraoperative brain maps, pre and postoperative imaging, we analyzed data correlations.

In this study, patients especially with obstructive sleep apnea and obesity (BMI > 30) were treated with a laryngeal mask (LMA) to control hypercapnia. Patients with a history of depression and emotional instability were preoperatively treated with antidepressants and mood-stabilizing medications.

Electrical stimulation mapping (ESM)

Stimulation is delivered by a electrodes pacing of 5 mm, by a bipolar biphasic current generator delivering a pulse duration of 1 ms in 4 second trains at 60 Hz. ESM starts from 2 mA to a maximum of 6 mA until induced somatosensory or motor function, or detection of potentials after discharge on intraoperative electrocorticography (ECoG) during language mapping [4,16,17]. The current used should be 1 mA less than that which evokes after-discharge potentials to a maximum of 6 mA, and the typical current used for sensorimotor functions (STIsm) was in the range of [2-3mA]. Therefore, the occurrence of ESM-induced seizures was avoided by using iced Ringer's solution [18].

Statistical data

R software, version 3.6.1, was used to analyze the statistical data (R Foundation for Statistical Computing, Vienna, Austria; URL: https://www.R-project.org/). Effectiveness and frequency for descriptive statistics are provided, along with a 95% confidence intervals (CIs). For the ESM threshold, the continuous variables were expressed as median and mean with standard deviation (sd). The differences were significant if the p-value was less than 5%.

RESULTS

Analysis of the outcome data shows that the median patient age was 49 years old in a range of [13 - 70], functional mapping was performed in language areas for 96% of patients and motor functions for 54%. In addition, (55.5% of the patients had high-grade tumors, 40.5% had low-grade tumors, and 4% had additional lesions (AVMs). Most lesions were in the temporal area (40.5%), followed by the frontal area (31%), 24.5% for insular area, 4% for the parietal area, and 85% of patients had left-sided lesions.

Referring respectively to ASA classification, Mallampati and KPS score, the majority of patients (73%) had mild systemic disease (ASA class 2), while 19% had severe systemic disease (ASA class 3). However, 6.7% of patients were healthy (ASA class 1), and only 1.3% were in critical condition (ASA class 4). Also, in 58% of patients, preoperative airway analysis revealed complete visibility of the soft palate and uvula (Mallampati level 2), and 35% demonstrated incomplete visualization (Mallampati level 2). Finally, 57% of patients had KPS scores of 90-100, and 43% had KPS scores lower than 80. Also, 54% of patients in the BMI range [16.6 to 56] had a low median BMI (23.9), while 46% had a high BMI (> 24), 47.3% had a preoperative history of depression, 21.6% were active smokers, and 4.1% had a chronic cough at the time of awake craniotomy (Table 1).

TABLE 1. Demographic and clinical data of patients undergoing awake craniotomy (n = 74)

Parameters	Median	Range
Age (years)	49	13-70
Days of hospitalization	3	2-20
BMI	24	16.6-56
Clinical data	**Effectif**	**%**
BMI		
Low (< 23.9)	40	54
High (>24)	34	46
Cancelled process	2	2.7
Smokers	12	16.2
Preoperative anticonvulsant medications	50	67.6
Preoperative seizure history	52	70.3
Depression history	35	47.3
Chronic cough	3	4.1
ESM-induced seizures	30	40.5
Tumor typology		
High grade	41	55.5
Low grade	30	40.5
Other (AVMs)	3	4
Tumor location		
Temporal	30	40.5
Frontal	23	31
Insular	18	24.5
Parietal	3	4
Tumor side		
Left	63	85
Right	11	15
Motor mapping	40	54
Language mapping	71	96
Number of anticonvulsant medications		
0	6	8.12
1	45	60.8
2	18	24.32
3	5	6.76
ASA classification		
Class 1 : healthy patient	5	6.7
Class 2 : mild disease	54	73
Class 3 : severe disease	14	19
Class 4 : life-threatening disease	1	1.3
Mallampati score		
Level 1	26	35
Level 2	43	58
Level 3	4	5.5
Level 4	1	1.5
KPS score		
< 80	32	43
90-100	42	57

Anesthesia and use of the LMA

The awake surgery monitored anesthesia care using the drug regimens propofol plus fentanyl, and the LMA was used for all patients (n = 74) to complete the mapping and maximize safety. Analysis of Table 2 revealed no correlation between the sedation technique and LMA use, typology of tumor, tumor location, ESM-induced seizures, tumor side, ASA classification, Mallampati score, patient BMI, or process cancellation.

Electrical stimulation mapping (ESM)

In all patients, the intraoperative ECoG was used to determine the ESM intensity, which was performed at a current between 2 and 6 mA. According to the outcomes of ESM, our study was divided into two groups: *group 1* and *group 2***.** So, Figure 1 reveals that the frequency of occurrence and the functional recovery time (FRT) of temporary convulsive seizures were highly significant in STIsm from 2.5 to 6 mA in *group 2***,** whereas there were no or brief seizures with threshold stimulation currents in a range of [2.35-2.45mA] in *group 1* (Table 3). Thereby, reducing the current to less than 2.35 mA causes a mapping objectified as a false-negative which does not protect patients and deprives them of benefiting from a maximalist functional neuro-oncology exeresis without malignant transformation. Furthermore, a current of 2.45 mA, as well as 2.35 mA, was well tolerated and was not associated with the occurrence of postoperative neurological deficits. Statistical analysis by Student T-test reveals that in a 95% confidence interval of [2.35, 2.45], the stimulation threshold intensity (STI) was 2.4 ± 0.05 mA in sensorimotor mapping. In contrast, there is a significant correlation coefficient (CC) of 0.79 between the intraoperative seizures, recovery time, and the STIsm.

ESM-induced seizures

While the incidence of ESM-induced seizures in the literature ranged from 2.2% to 21.5% [18,19], in our series of 70.3% in antecedent preoperative seizures, it was in 40.5% of patients in group 2 compared to 10.8% of patients in *group 1* (p = 0.01). All convulsive crises were terminated by the application of ice-cold Ringer's lactate serum, with the exception of one abortive ESM-induced total seizure.

Since 67.6% of patients were taking antiepileptic drugs prior to surgery, the majority of cases were on a single drug regimen (60.8%), 31.1% used two or more antiepileptic drugs, and ESM-induced seizures occurred in 4.05% in *group 1* versus 30.5% in *group 2***.** So, there is no correlation between the occurrence of ESM-induced seizures and antiepileptic drug use, tumor type, or BMI. Indeed, occurrence of ESM-in-

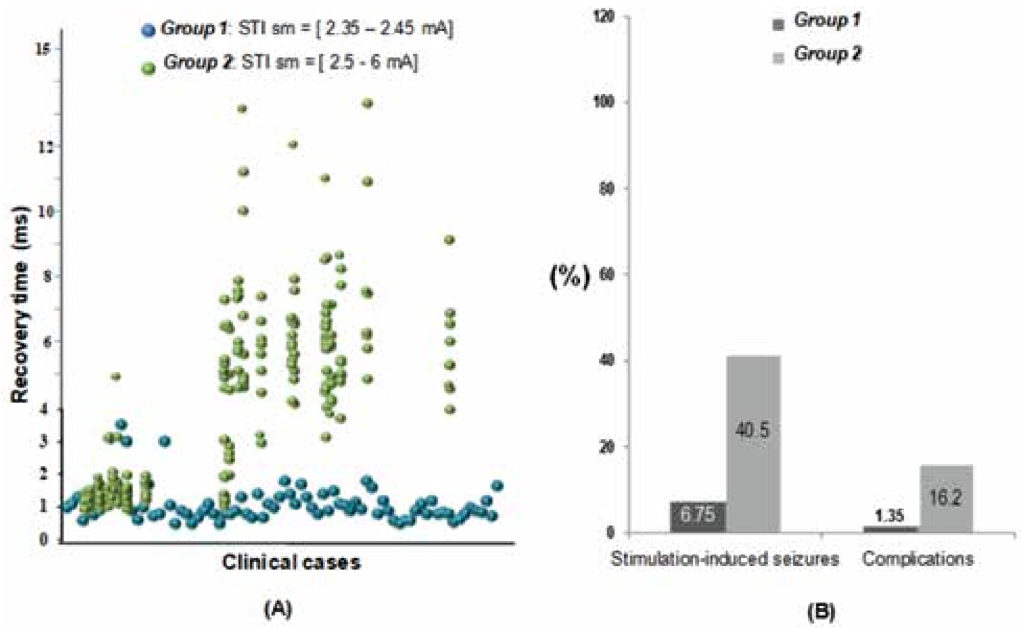

FIGURE 1. (A) shows that in intraoperative care, the recovery time after transient seizures during resection varied between 1 s and 13 s for group 2, while the stimulation reduced this time up to a median of 1.5 s for series 1. (B) For group 1, pacing at [2.35–2.45 mA] results in fewer transient seizures (6.75%), which are quickly controlled within 1s to 3s, whereas stimulation at [2.5-6mA] explains the occurrence of temporary seizures in 40.5% and the recovery time, which increases and fluctuates significantly up to 13 ms. The assessment of complications shows that they happened much less often in group 1 (1.35%) than 16.2% in group 2, where the intensity was higher

duced seizures was significantly higher against the preoperative seizure history and the tumor location (frontal and temporal lesion in the first place; p = 0.002; Table 2).

TABLE 2. Assessment of ESM-induced seizures in peroperative care

Parametrs	ESM *group 1* (n = 40)		ESM *group 2* (n = 34)		p-Value
	Effectif	%	Effectif	%	
Preop* seizures	5	6.75	30	40.5	0.01
Preop anticonvulsant	3	4.05	27	36.5	0.12
Tumor location					0.002
Temporal	2	40	10	29.4	
Frontal	1	20	14	41.2	
Parietal	1	20	7	20.6	
Insular	1	20	3	8.8	
Tumor typology					0.84
High grade	2	40	21	61.8	
Low grade	2	40	13	38.2	
Other	1	20	0	0	
BMI					0.10
Low (< 23.9)	1	20	10	29.4	
High (> 24)	4	80	24	70.6	

** Preop: preoperative*

COMPLICATIONS AND FAILURE RATE

In intraoperative care, the complication rate was significantly higher for *group 2* compared to *group 1*, with 16.2% in *group 2* versus 1.35% in *group 1*, and a readmission rate of 1.35% for all groups, including early neurological deficits (14.7% versus 2.5%) and late neurological deficits (23.7% versus 2.5%). Postoperative complications were more prevalent in patients of *group 2* with aborted mapping (1.35%, p = 0.03) and ESM-induced seizures (20.3%, p = 0.003). In this case, 50% of the global attacks induced by stimulation were complicated only in group 2 with high STIsm intensity. 83.3% of smokers had complications, including 13.5% in *group 2* against only 2.7% in *group 1*.

The inability to complete the ESM (aborted mapping) and safety resection was defined as an awake craniotomy failure. In perioperative care, functional mapping was aborted in two cases (2.7%) in group 2 due to occurrence of seizures (1 case) and quality of awakening resulting from anesthesia (1 case). So, one patient's ESM-induced seizures were poorly controlled with iced Ringer's solution; therefore, the craniotomy was closed by common resection in the asleep mode. The resection for the other case was performed using available mapping data combined with neuronavigation.

According to the awake craniotomy failure rate reported in the literature, which ranges between 2.3% and 6.4% [1,20], our failure rate was only 2.7%. While smoking has long been associated with poorer postoperative outcomes in neurosurgery and a higher prevalence of depression [21], in our study, 16.2% of patients were active smokers, and 25.7% of them had depression disease compared to 42% of nonsmoking depressive patients (p = 0.001), as were those with chronic cough, with 5.7% of smokers compared to 1.6% of nonsmokers (p = 0.01). However, there was no significant difference in adverse intraoperative outcomes for 2.7% of smokers in *group 1* and 13.5% in *group 2* against 24.3% of non-smokers (p = 0.75). So, the threshold intensity remained a triggering factor for seizures for smokers in *group 2* (Table 3).

TABLE 3. Assessment of the occurrence of neurological deficits and complications during patient care

Parametrs	ESM *group 1* (n = 40)		ESM *group 2* (n = 34)		p-Value
	Effectif	%	Effectif	%	
Tumor typology					0.55
High grade	20	50	11	64.7	
Low grade	1	25	6	35.3	
Other	1	25	0	0	
Tumor location					0.73
Temporal	2	50	7	41.2	
Frontal	1	25	6	35.3	
Insular	1	25	2	11.75	
Parietal	0	0	2	11.75	
ASA classification					0.2
Class 1	1	25	3	17.7	
Class 2	2	50	9	53	
Class 3	1	25	5	29.3	
Class 4	0	0	0	0	
Mallampati score					0.61
Level 1	1	25	5	29.4	
Level 2	2	50	8	47.1	
Level 3	1	25	4	23.5	
Level 4	0	0	0	0	
Intraoperative seizures rate	1	1.35	12	16.2	
Early deficit at discharge	1	1.35	5	6.75	
Infection	0	0	1	1.35	
Hemorrhage	0	0	1	1.35	
Postoperative stroke	0	0	3	4.05	
Late/residual deficit	0	0	8	10.8	
ESM-induced seizure	0	0	15	20.3	0.002
Smoker	2	2.7	10	13.5	0.1
Aborted mapping	0	0	1	1.35	0.02

DISCUSSION

Statistical analysis of outcome data has remained a promising approach to define limiting factors in the characterization for successful awake craniotomies by sensorimotor and language mapping in order to maximize intraoperative safety and improve the extent of the resection (EOR). For this reason, and to achieve improved reliability and fidelity in this work, intraoperative ECoG was employed to optimize the ESM threshold with the goal of exceeding the boundary limit linked to false negative results for sensorimotor functions in STIsm>2.35 mA. So, the [2.35-2.45 mA] threshold intensity range was used to find the best mapping, which led to fewer seizures and a shorter recovery time.

In correlation with the literature data in Table 4 and the characteristics of our ESM, the threshold intensities agree perfectly within the better-defined range of *group 1*.

TABLE 4. Correlation between ESM reference parameters and our ESM threshold

ESM references	Pulse duration (ms)	Stimulation intensity (mA)
Berger et al	1	2-16
Thiebaut de Schotten et al	1	2-8
Rech et al	1	1-4
Bello et al	0.5	≥ 2
Our study	1	2.35-2.45

All practitioners used a bipolar biphasic current and 60 Hz in frequency

Our findings indicate that awake craniotomy can be performed by ESM safely under the threshold conditions with few complications and a low failure rate, as shown by the *group 1* results, and regardless of ASA classification, tumor site, tumor type, Mallampati and KPS score, BMI, smoking status, psychiatric and seizure history, or tumor mass effect in all groups.

Compared to published data with complication rates of 14-32% and failure rates of 2.3-6.4% [21,22], our best outcome for *group 1* shows a high degree of success and has a very low failure rate (2.7%). Also, the ESM-induced seizures were the most common factor for failure (50%), this demonstrates the importance of managing crises before and during surgery to keep patients safe, as well as using threshold pacing. So, for *group 1*, the application of the ESM threshold in the range [2.35-2.45mA] in line to our flowchart justifies the quality of the obtained results and serves as a reference standard whose efficacy has been demonstrated during sensorimotor mapping. Therefore, it can enhance sensitivity by transcending the limitations imposed by stimulation beyond threshold settings (Figure 2, Table 5).

LIMITATIONS

The limitations have been summarized in the small number of clinical cases and lack of electrical mapping standard. To overcome these limitations, we take enough time during the direct electrical stimulation in the functional mapping to have precise current threshold intensities. Also, stimulation

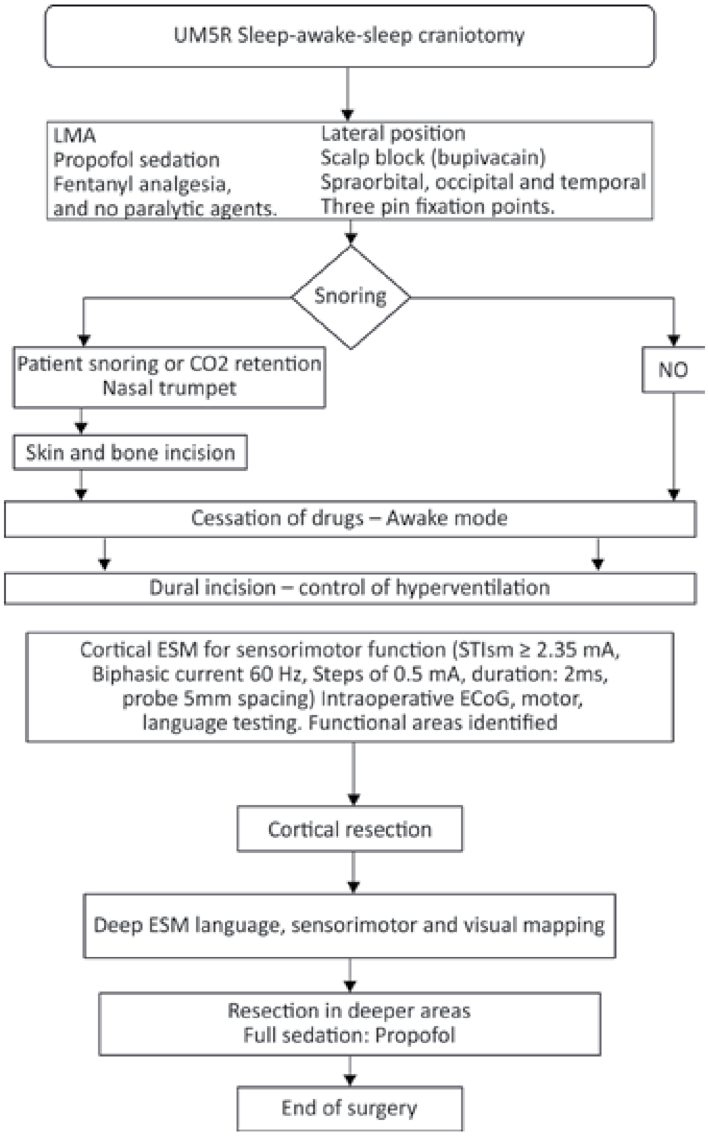

FIGURE 2. UM5R awake craniotomy flowchart

TABLE 5. The comparison of the outcome performances of the literature with those of our study

Outcomes		Number of cases	Intraoperative seizures (%)	Failure rate (%)	Complications (%)
Trinh et al		214	NS	NS	ND (41)
Grossman et al		90	2.2	NS	ND (22.7), HMG (3.3)
Pereira et al		79	21.5	2.5	SK (6.3), INF (2.5)
Gignac et al		30	16.7	NS	NS
Our study	*Group 2*	34	40.5	1.35	ND (17.6), HMG (1.35), SK (4.05), INF (1.35)
	Group 1	40	6.75	1.35	ND (1.35)

HMG: hemorrhage, INF: infection, ND: neurological deficit, NS: not stated in study, SK: stroke

feedback was exploited by the coupling of ECoG and neurophysiologist confirmation.

CONCLUSIONS

The analysis's findings indicate that awake craniotomy with an adequate EMS threshold in the range of [2.35-2.45mA] was a secure and efficient alternative with no significant failure rates or neurological complications. Except infiltrating tumors, the findings were not related to internal factors affecting the patients. As a result, EMS threshold conditions and pacing-induced seizure management are critical for advantageous resection promoting performance and the desired results.

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