Tzu Chi Medical Journal 2021; 33(4): 395-398

Original Article

Correlation between intraoperative mapping and monitoring and functional outcomes following supratentorial glioma surgery

*Han-Lin Wu[a], Po-Cheng Hsu[b], Sanford P. C. Hsu[c], Chun-Fu Lin[c], Kwong-Kum Liao[c], Kai-Ming Yang[a], Chen-Liang Chou[a], Tsui-Fen Yang[a]**

[a]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, Taipei, Taiwan; [b]Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Bei-Hu Branch, Taipei, Taiwan; [c]Department of Neurosurgery, The Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

Submission : 30-Oct-2020
Revision : 08-Dec-2020
Acceptance : 08-Jan-2021
Web Publication : 05-Apr-2021

Abstract

Objectives: Intraoperative neurophysiological monitoring (IONM) has long been regarded as the "gold standard" when resecting a supratentorial glioma, as it facilitates the goals of maximal tumor resection and preservation of sensorimotor function. The purpose of the present study was to evaluate the ability of motor evoked potentials (MEPs) monitoring or subcortical mapping (SCM), alone or in combination, to predict postoperative functional outcomes in glioma surgery. **Materials and Methods:** We retrospectively reviewed patients with supratentorial glioma that underwent craniotomy for tumor removal with IONM. Statistical analyses were used to evaluate whether the following criteria correlated with postoperative functional outcomes: Reduced amplitude (>50% reduction) or disappearance of MEPs (criterion 1), SCM with a stimulation intensity threshold less than 3 mA (criterion 2), the presence of both two phenomena (criterion 3), or either one of the two phenomena (criterion 4). **Results:** Ninety-two patients were included in this study, of whom 15 sustained new postoperative deficits, 4 experienced improved functional status, and 73 were unchanged. Postoperative functional status correlated significantly with all four criteria, and especially with criterion 3 (r = 0.647, P = 0.000). Sensitivity of IONM was better if using criteria 2 and 4, but specificity was better if using criteria 1 and 3. Criterion 3 had the most favorable overall results. **Conclusion:** Using statistical methodology, our study indicates that concomitant interpretation of MEPs and SCM is the most accurate predictor of functional outcomes following supratentorial glioma surgery. However, accurate interpretations of the monitoring results by experienced neurophysiologists are essential.

Keywords: *Functional outcome, Intraoperative neurophysiological monitoring, Motor evoked potentials, Subcortical mapping*

Introduction

Supratentorial brain tumors are a principal cause of major morbidity and mortality worldwide [1]. Glioma is the most common pathological type of supratentorial brain tumor and is broadly divided into low-grade (World Health Organization [WHO] grade II) and high-grade (WHO grades III-IV). Low-grade gliomas have a strong propensity to malignant transformation and local spread along white matter tracts, despite their slow-growing nature [2]. Due to ongoing advancements in the field, the treatment of gliomas has experienced a paradigm shift towards a more active approach to management. Both long-term oncologic and functional outcomes are positively correlated with the extent of resection (EOR) [3]. Given the tendency of gliomas to develop and progress near eloquent brain structures, intraoperative neurophysiological monitoring (IONM) and mapping techniques are important to reduce the risk of injury to neurologically vital areas; this is particularly true given the current trend to pursue more aggressive treatments for this population group [1,4-6]. Maximal safe resection according to functional boundaries, guided by IONM, is now the standard treatment for low- and high-grade gliomas involving eloquent areas [7].

There are two major intraoperative neurophysiological techniques for assessing motor function and safety of

Access this article online	
Quick Response Code:	Website: www.tcmjmed.com
	DOI: 10.4103/tcmj.tcmj_270_20

**Address for correspondence:*
Dr. Tsui-Fen Yang,
Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, 201, Section 2, Shipai Road, Beitou District, Taipei, Taiwan.
E-mail: tfyang@vghtpe.gov.tw

How to cite this article: Wu HL, Hsu PC, Hsu SP, Lin CF, Liao KK, Yang KM, *et al.* Correlation between intraoperative mapping and monitoring and functional outcomes following supratentorial glioma surgery. Tzu Chi Med J 2021; 33(4): 395-8.

resection: Motor-evoked potentials (MEP), obtained with transcranial or direct cortical stimulation (TCS or DCS, respectively), and subcortical mapping (SCM), which determines the distance between the stimulation point and the corticospinal tract (CST). It is widely accepted that there is a linear relationship of 1 mA per 1 mm of brain tissue, i.e., the distance between the current resection cavity and the CST in millimeters is roughly the same as the subcortical stimulation intensity threshold (in milliamperes) to elicit a motor response [8,9]. Typically, cessation of the surgical resection is suggested when an intensity threshold is <3 mA using a monopolar stimulation probe. During MEP monitoring, most recognize an amplitude drop of 50% or more as an important indicator of potential damage to the motor pathway [10]. These two widely used approaches can be complementary and be used together.

To the best of our knowledge, there has been no previously published work using statistical analyses to evaluate which of these two monitoring techniques, either used alone or in combination, can best predict postoperative neurological outcomes following supratentorial glioma surgery. The purpose of the present study was to determine which monitoring indicators correlate best with postoperative functional outcomes and can thus be used reliably to guide surgical resection of supratentorial gliomas. Our hypothesis is that combining both monitoring and mapping techniques would allow surgeons to safely maximize the EOR. We aimed to utilize statistical analyses to substantiate this hypothesis.

Materials and methods

We retrospectively reviewed patients with supratentorial glioma that underwent craniotomy for tumor resection with IONM. In addition to imaging studies, all patients underwent thorough physical and neurological examinations (including motor and sensory functional status) before and after surgery, and prior to discharge. Manual muscle testing (MMT, grade 0–5) was used to assess muscle strength of the affected limbs and the Barthel Index (BI) was used to measure performance in activities of daily living. More than one grade deterioration in MMT and reduction of >10 score in BI were defined as new functional deficit after operation. This study was approved by the Institutional Review Board of our hospital (2018-06-020AC, approved on June 1, 2018). Informed written consent was waived because the study was a retrospective data analysis.

Total intravenous anesthesia with propofol and remifetanyl was used during surgical procedures, and only one dose of muscle relaxant was used, during induction only. Depth of anesthesia was kept at a consistent level by an anesthesiologist so that IONM could be performed continuously. After craniotomy, phase reversal was applied to identify the central sulcus and to define the sensorimotor cortex, if indicated. Cortical mapping was then used to define the location of the eloquent motor cortex. While surgeons were resecting the tumor, we used somatosensory evoked potential and MEP monitoring, by either TCS or DCS, to safeguard the integrity of the sensorimotor function. MEP monitoring was performed with intermittent multi-pulse train stimulation (4–9 pulses, 50 us pulse duration, 500 Hz, 50–100 V for DCS and 180–300 V for TCS). SCM, using a monopolar electrode and multi-pulse train stimulation technique (5 pulse, 500 us, 500 Hz, 0.1–15 mA), was used to identify the proximity of the subcortical motor tract during the resection, whenever surgeon requested. IONM in the present study was conducted using 32 channel IONM system, Cascade Elite.

After collecting all related data from medical records, we then used statistical analyses to investigate for a relationship between postoperative functional outcomes and the following criteria during surgery: Reduced amplitude (>50% reduction) or disappearance of MEPs (criterion 1), SCM with a stimulation intensity threshold <3 mA (criterion 2), presence of both two phenomena (criterion 3), or either one of the two phenomena (criterion 4). Statistical indicators used to evaluate the strength and weakness of aforementioned four criteria included sensitivity, specificity; diagnostic odds ratio (DOR), receiver operating characteristic (ROC) curve, area under the ROC curve (AUC); positive predictive value (PPV), negative predictive value (NPV); false-positive rate (FPR), false-negative rate (FNR); positive likelihood ratio (PLR), negative likelihood ratio (NLR). DOR is the ratio of the probability of positivity in patients with neurological injury during operation relative to the probability in patients without injury. It is a global measure for diagnostic accuracy and is used for comparison between multiple diagnostic tests. ROC curve is a graph plotted with sensitivity on the y-axis and 1-specificity on the x-axis. AUC is the AUC with a range of value between 0 and 1 and is a useful indicator of the discriminative power of a test. An AUC of >0.7 designates good diagnostic accuracy. PPV is the probability of a true neurological injury in a patient with positive result. On the other hand, NPV is the probability of absence of neurological injury in a patient with negative result. PLR is the ratio of sensitivity to 1-specificity, the value of which of >10 indicates good diagnostic test. NLR is the ratio of 1-sensitivity to specificity, the value of which of <0.1 is considered good.

Results

Demographics

Ninety-two patients with supratentorial glioma who underwent craniotomy for tumor resection were included in this study (46 males and 46 females, age range: 2.5–85 years old [mean age: 45.0 ± 17.4 years]).

Postoperative outcomes

Of the 92 patients in our study, 15 patients sustained new deficits after surgery, 4 patients experienced an improved functional status after surgery, and 73 patients were unchanged postoperatively. In 12 patients, MEPs decreased significantly or disappeared irreversibly before the end of the procedure, and 7 of these sustained new postoperative functional deficits. During SCM, the intensity used to elicit compound motor action potentials from the contralateral muscles ranged from 0.5 to 20 mA (mean: 5.4 ± 4.1 mA); in 33 patients, a stimulation intensity threshold lower than 3 mA was used, and of these, 13 patients experienced a functional deterioration after surgery. There were 9 patients with both significant MEP changes and a SCM stimulation intensity threshold of <3 mm during surgery, and 8 of them sustained new postoperative functional deficits. Of the 37 patients with either significant MEP changes or a SCM stimulation intensity threshold of <3 mA during surgery, 13 experienced new neurological deficits following surgery. Seven patients sustained new functional deficits although SCM reading was higher than 3 mA and their MEP had stayed stable till the end of procedure. Postoperative magnetic resonance imaging (MRI) study did reveal acute cerebral infarction which might occur at immediate postoperative stage in all of them.

Diagnostic accuracy

The mean SCM values in the groups with and without new postoperative deficits were 2.27 ± 1.12 and 5.99 ± 4.19, respectively, and this difference was statistically significant according to the Mann–Whitney U-test. The age and gender of patients did not show a significant correlation with surgical outcomes. Using Spearman's correlation, postoperative functional status correlated significantly with all four criteria, and especially with criterion 3 (r = 0.647, P = 0.000). The sensitivity of IONM was better when using criteria 2 and 4; however, specificity was better if using criteria 1 and 3 [Table 1]. There appeared to be strengths and weaknesses for each single criterion, but criterion 3 was noted to possess more advantages than others when using statistical analysis to calculate DOR, AUC, PPV, NPV, FPR, and PLR.

Discussion

Current surgical strategies toward supratentorial glioma

Removal of a supratentorial glioma does carry the risk of creating new functional deficits, since the aim of surgery is to remove as much of the tumor as possible, with the goal of maximizing long-term survival. Accumulated evidence has indicated that overall survival (OS) and progression-free survival (PFS) is largely determined by the EOR [4,5,11]. An EOR of >90% has been found to be significantly related to positive effects on both OS and PFS [12]. A more radical and relatively new concept in neuro-oncological surgery, known as supratotal resection (defined as resection beyond the margins of the tumor on MRI), has been shown to improve outcomes by delaying malignant transformation or recurrence [13-15]. Nonetheless, a wider EOR conventionally carries a greater risk of neurological injury because gliomas commonly involve eloquent areas of motor cortex or the CST. This combination of the infiltrative nature of gliomas, with more aggressive surgical strategies, have made intraoperative monitoring and mapping essential in the resection of gliomas, to preserve neural integrity and to maximize postoperative functional outcomes [3].

Table 1: Results of our study

	Criterion 1 (MEP)	Criterion 2 (SCM)	Criterion 3 (MEP + SCM)	Criterion 4 (MEP or SCM)
Sensitivity (%)	46.7	86.7	53.3	86.7
Specificity (%)	93.5	74.0	98.7	68.8
DOR	12.6	18.5	86.9	14.3
AUC	0.701	0.803	0.760	0.777
PPV (%)	58.3	39.4	88.9	35.1
NPV (%)	90.0	96.6	91.6	96.4
FPR (%)	41.7	60.6	11.1	64.9
FNR (%)	10.0	3.4	8.4	3.6
PLR	7.1	3.3	41	2.7
NLR	0.5	0.1	0.4	0.1

MEP: Motor evoked potential, SCM: Subcortical mapping, DOR: Diagnostic odds ratio, ROC: Receiver operating characteristic, AUC: Area under the ROC curve, PPV: Positive predictive value, NPV: Negative predictive value, FPR: False-positive rate, FNR: False-negative rate, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio

Two commonly used intraoperative monitoring techniques

In clinical practice, MEP monitoring with either TCS or DCS, and SCM with a monopolar probe, are the two major techniques for ensuring safe resection without injuring motor systems [10,11,16]. Each has its own strengths and weaknesses. Most monitoring specialists consider a >50% amplitude loss of MEP as critical. As for SCM, a linear correlation between motor threshold (MT) intensity in milliamperes and the distance of stimulation point to the CST in millimeters is well established [8,17]. With the current trend of more active and even preemptive surgical strategies for gliomas, it is imperative to find out which criteria are more clinically relevant, and in particular, which are more strongly associated with postoperative neurological deficits and functional outcomes. According to our analyses, combining both MEP monitoring and MT on SCM offered the optimal overall prediction. The criterion 3 provided the highest values of DOR, PPV, and PLR, much higher than those of all other three criteria. Furthermore, the criterion had the lowest value of FPR among the four criteria, while performing well at AUC and NPV.

Previous studies have recommended that combined guidance with both MEP and SCM not only improves the safety of surgery but also increases the extent of surgical resection [1,12,16,18]. However, the strengths and weaknesses of each of these modalities have not been thoroughly studied with statistical analysis thus far, and there is no doubt that this information will offer important information to the relevant professionals. Whenever choosing a diagnostic tool in clinical practice, we need to look closely into both the sensitivity and specificity of that particular tool. However, frequently, a higher sensitivity is associated with a lower specificity, due to a higher FPR. During surgery for supratentorial gliomas, there are two possible causes of new postoperative deficits. One is direct injury, due to resection too close to the subcortical motor tract, and this phenomenon is frequently encountered when SCM readings are lower than 3 mA. The other cause is mediated through interruption of the blood supply to the subcortical motor tract during surgery, including through vasospasm during manipulation. We maintained a safe distance between the area of resection and the subcortical motor tract, aiming for SCM readings >3 mA, although MEPs can still decrease or disappear during IONM due to ischemia. This is one of the reasons for discrepancies between MEP and SCM monitoring. The sensitivity of MEPs was 46.7% and specificity was 93.5% in our series. The low sensitivity may be due to a time gap, in that motor deterioration may have actually happened after the end of the surgical procedure and IONM, either from the interruption of blood flow or the development of focal edema. The sensitivity of SCM was 86.7% and the specificity was 74% in our series, and the AUC was 0.803. As such, SCM monitoring appears to be an excellent tool to discriminate groups with and without new postoperative deficits. Criterion 3 possessed low sensitivity (53.3%) and extremely high specificity (98.7%), along with a low FPR (11.1%), and this implied that it is a stricter criterion to use to identify patients with new postoperative deficits. Criterion 4 appeared to have the opposite characteristics, with a high sensitivity (86.7%) and a low specificity (68.8%) along with a remarkably high FPR (64.9%), which suggests that it may not be useful for guidance during surgical resection.

Implications for practice

The DOR and AUC are statistical analyses that account for both sensitivity and specificity. An ideal diagnostic tool should possess high predictive value, low false rate, high PLR, and a low NLR. Thus, in our series, surgical resection of a glioma under the guidance of criterion 3 appears to have more advantages than the other three criteria, given that it possessed a higher DOC (86.9), acceptable AUC (0.760), high PPV (88.9%), high NPV (91.6%), low FPR (11.1%), and high PLR (41) compared to others. However, given that criterion 3 is a stricter criterion to use to define the existence of a possible postoperative deficit, it will have a higher FNR (8.4%). Therefore, consideration of the concomitant use of other criteria based on the specific clinical situation is still recommended, whenever indicated.

Conclusion

Using statistical methodology, our study shows that concomitant interpretation of MEPs and SCM is the most accurate predictor of functional outcomes following supratentorial glioma surgery. However, given the suboptimal sensitivity and FNRs of this approach in clinical practice, it certainly highlights the importance of accurate interpretations of the monitoring results by experienced neurophysiologists.

Financial support and sponsorship

This study was supported by a grant from Taipei Veterans General Hospital (V108C-017).

Conflicts of interest

There are no conflicts of interest.

References

1. Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. J Neurooncol 2016;130:269-82.
2. Lima GLO, Dezamis E, Corns R, Rigaux-Viode O, Moritz-Gasser S, Roux A, et al. Surgical resection of incidental diffuse gliomas involving eloquent brain areas. Rationale, functional, epileptological and oncological outcomes. Neurochirurgie 2017;63:250-8.
3. Zhang N, Yu Z, Hameed NU, Xu G, Song Y, Wu B, et al. Long-term functional and oncologic outcomes of glioma surgery with and without intraoperative neurophysiologic monitoring: A retrospective cohort study in a single center. World Neurosurg 2018;119:e94-e105.
4. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008;26:1338-45.
5. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115:3-8.
6. Senft C, Forster MT, Bink A, Mittelbronn M, Franz K, Seifert V, et al. Optimizing the extent of resection in eloquently located gliomas by combining intraoperative MRI guidance with intraoperative neurophysiological monitoring. J Neurooncol 2012;109:81-90.
7. Plans G, Fernández-Conejero I, Rifà-Ros X, Fernández-Coello A, Rosselló A, Gabarrós A. Evaluation of the high-frequency monopolar stimulation technique for mapping and monitoring the corticospinal tract in patients with supratentorial gliomas. A proposal for intraoperative management based on neurophysiological data analysis in a series of 92 patients. Neurosurgery 2017;81:585-94.
8. Nossek E, Korn A, Shahar T, Kanner AA, Yaffe H, Marcovici D, et al. Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation. Clinical article. J Neurosurg 2011;114:738-46.
9. Prabhu SS, Gasco J, Tummala S, Weinberg JS, Rao G. Intraoperative magnetic resonance imaging-guided tractography with integrated monopolar subcortical functional mapping for resection of brain tumors. Clinical article. J Neurosurg 2011;114:719-26.
10. Krieg SM, Shiban E, Droese D, Gempt J, Buchmann N, Pape H, et al. Predictive value and safety of intraoperative neurophysiological monitoring with motor evoked potentials in glioma surgery. Neurosurgery 2012;70:1060-70.
11. Saito T, Muragaki Y, Maruyama T, Tamura M, Nitta M, Okada Y. Intraoperative functional mapping and monitoring during glioma surgery. Neurol Med Chir (Tokyo) 2015;55:1-13.
12. Tamura M, Muragaki Y, Saito T, Maruyama T, Nitta M, Tsuzuki S, et al. Strategy of surgical resection for glioma based on intraoperative functional mapping and monitoring. Neurol Med Chir (Tokyo) 2015;55:383-98.
13. Motomura K, Chalise L, Ohka F, Aoki K, Tanahashi K, Hirano M, et al. Supratotal resection of diffuse frontal lower grade gliomas with awake brain mapping, preserving motor, language, and neurocognitive functions. World Neurosurg 2018;119:30-9.
14. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: A consecutive series with 11-year follow-up. Acta Neurochir (Wien) 2016;158:51-8.
15. Delgado-López PD, Corrales-García EM, Martino J, Lastra-Aras E, Dueñas-Polo MT. Diffuse low-grade glioma: A review on the new molecular classification, natural history and current management strategies. Clin Transl Oncol 2017;19:931-44.
16. Moiyadi A, Velayutham P, Shetty P, Seidel K, Janu A, Madhugiri V, et al. Combined motor evoked potential monitoring and subcortical dnamic Mmapping in motor eloquent tmors aAllows safer and extended resections. World Neurosurg 2018;120:e259-e68.
17. Shiban E, Krieg SM, Haller B, Buchmann N, Obermueller T, Boeckh-Behrens T, et al. Intraoperative subcortical motor evoked potential stimulation: How close is the corticospinal tract? J Neurosurg 2015;123:711-20.
18. Barone F, Alberio N, Iacopino DG, Giammalva GR, D'Arrigo C, Tagnese W, et al. Brain mapping as helpful tol in Bbain Gglioma surgical treatment-toward the "Perfect Surgery"? Brain Sci 2018;8:192.