Neurosurgery

Evaluation of the High-Frequency Monopolar Stimulation Technique (HFMS) 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

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Abstract:	Background: Intraoperative identification and preservation of the corticospinal tract (CST) is often necessary for glioma resection. Object: To make a proposal for intraoperative management with the high-frequency monopolar stimulation technique (HFMS) for monitoring the CST. Methods: 92 patients operated on with the assistance of the HFMS. Clinical and neurophysiological data have been related with the motor status at 3 months to establish prognostic factors of motor deterioration. Results: 21 patients (22,8%) presented intraoperative alterations in motor evoked potentials (MEPs). Twelve (13%) presented an increment in the MEP threshold ≥5 mA (no deficit at 3 months). Two (2,2%) presented a MEP amplitude reduction > 50% (100% deficit at 3 months). Seven (7,6%) had an intraoperative MEP loss (80% deficit at 3 months). Subcortical stimulation was positive in 75 patients (81,5%). 85 patients were available for the analysis at 3 months. Fourteen presented new deficits (16,5%). Among them, five presented a deficit in non-monitored muscles (5,9%) and one presented a new deficit not detected intraoperatively. The combination of patients with preoperative motor deficits, MEP deterioration or loss and intensity of subcortical stimulation ≤ 3mA showed the highest sensitivity and specificity in the predicition of new deficits Conclusions: Persistent MEP loss or deterioration is associated with a high probability of new deficits. It seems recommendable to stop the subcortical resection before obtaining a subcortical MEP threshold at 3mA especially in patients with preoperative motor deficits A careful selection of muscles for the registration of MEPs is mandatory to avoid deficits in non-monitored muscles.
Additional Information:	
Question	**Response**
Significance of the Work: Please include a brief statement summarizing the significance of the work and in particular how it differs from and advances existing literature.	The high-frequency monopolar stimulation technique (HFMS) has emerged in recent years as a useful tool for intraoperative neuromonitoring (IONM) during neurosurgical procedures. Some papers have been published demonstrating its usefulness for mapping and monitoring motor structures during tumor resection. However, intraoperative warning criteria are reported to be quite variable between the

	authors, especially with respect to the subcortical-safe MEP threshold. In this paper we will describe the intraoperative methodology used for IONM with this technique in 92 patients with supratentorial gliomas. A proposal for intraoperative management with the HFMS is also made in the paper, based on intraoperative data analysis and its relation with permanent motor deficits at 3 months. Our results are compared in the discussion with the current existing data published in the literature with the final intention to propose objective criteria to assist neurosurgical procedures using this technique. We expect that this paper will help to add more knowledge to the current existing literature with respect to IONM procedures used in patients with gliomas.
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ABSTRACT

Background: Intraoperative identification and preservation of the corticospinal tract is often necessary for glioma resection.

Object: To make a proposal for intraoperative management with the high-frequency monopolar stimulation technique for monitoring the corticospinal tract.

Methods: Ninety-two patients operated on with the assistance of the high-frequency monopolar stimulation. Clinical and neurophysiological data have been related with the motor status at 3 months to establish prognostic factors of motor deterioration.

Results: Twenty-one patients (22.8%) presented intraoperative alterations in motor evoked potentials (MEPs). Twelve (13%) presented an increment in the MEP threshold ≥ 5 mA (no deficit at 3 months). Two (2.2%) presented a MEP amplitude reduction > 50% (100% deficit at 3 months). Seven (7.6%) had an intraoperative MEP loss (80% deficit at 3 months). Subcortical stimulation was positive in 75 patients (81.5%).

Eighty-five patients were available for the analysis at 3 months. Fourteen presented new deficits (16.5%). Among them, 5 presented a deficit in non-monitored muscles (5.9%) and 1 presented a new deficit not detected intraoperatively.

The combination of patients with preoperative motor deficits, MEP deterioration or loss and intensity of subcortical stimulation ≤ 3 mA showed the highest sensitivity and specificity in the predicition of new deficits

Conclusions: Persistent MEP loss or deterioration is associated with a high probability of new deficits.

It seems recommendable to stop the subcortical resection before obtaining a subcortical MEP threshold at 3 mA especially in patients with preoperative motor deficits

A careful selection of muscles for the registration of MEPs is mandatory to avoid deficits in non-monitored muscles.

Short Title: IONM of the Corticospinal Tract With the High-Frequency Monopolar Stimulation Technique in Gliomas

Keywords: High-frequency Stimulation; Monitoring; Corticospinal Tract; Glioma

Surgical treatment of gliomas in the central region of the brain carries a significant risk of postoperative morbidity. Postoperative motor deficits vary between 4-17%[1-8] depending on different factors such as tumor type, location, intraoperative methodology used, and extent of resection. Complete resection should be the goal of the surgical treatment, but this is not always possible due to the ability of these tumors to infiltrate eloquent regions of the brain without causing neurological symptoms, especially in the case of low-grade gliomas. A complete resection of the measurable tumor on MRI has demonstrated to have a positive impact on patients survival and quality of life but there is also evidence that maximal resections have a positive impact on survival in both low-[9] and high-grade tumors.[10,11] This gives a place for the so-called functional resection of gliomas, ie, a maximal safe resection of tumors that infiltrate eloquent brain structures such as the motor areas, corticospinal tract (CST), or language areas. In these situations, the functional resection of the tumors may offer some benefits such as high accuracy of diagnosis, better epilepsy control, and a benefit in patients' survival and progression-free survival.[9-11] To perform this type of surgery an intraoperative technique to assess neurological function during the resection is of paramount importance.

The most widely used technique for mapping motor functions, either cortically or subcortically, is the 50 or 60 Hz bipolar stimuli initially described by Penfield[12] and developed later on by other authors.[3,13-15] Intraoperative management is clear, but the risk of intraoperative seizures and the impossibility to monitor the CST integrity during the resection can be considered as an important limitation of the technique. The high-frequency monopolar train-of-5 stimuli has been recently demonstrated as useful for mapping and monitoring brain motor functions during surgery. Some articles have been published in recent years describing intraoperative methodology and postoperative results. The technique was firstly described by Taniguchi in 1993[16] and consists of the use of a monopolar cortical stimulation probe or grid with a reference cathode to obtain a motor evoked potential (MEP). Its main strength is the ability to monitor the functional integrity of the CST during the surgery with a low incidence of seizures. Some authors have also demonstrated its usefulness for mapping the motor cortex[17-20] and the CST.[4,20-22] The positivity of the subcortical stimulation with this technique seems to be distance-dependant so that the subcortical MEP threshold reflects the distance between the stimulation point and the CST4.[7,23,24] Positive subcortical stimulation at high intensities may indicate that a safe resection of the tumor can be performed without a risk of lesioning the CST if cortical MEPs are stable. In contrast, positive stimulation at low intensities may advise stopping the resection due to an excess of proximity to the CST.

MEP loss during the resection is usually associated with a permanent deficit[5] but intraoperative warning criteria to stop the resection are not clearly defined and are variable between authors.[1,2,5,17,25] The subcortical safe-intensity is also not clearly defined.[4,7,22-24]

In this paper, we will describe the intraoperative methodology used during motor mapping and intraoperative neuromonitoring (IONM) in patients with supratentorial gliomas located in relation with the motor cortex and the CST using the high-frequency monopolar stimulation (HFMS) technique. Intraoperative data and its relation with permanent postoperative deficits will be analyzed and finally a proposal for intraoperative management will be made.

METHODS

Patients

A selection of patients was operated on between March 2009 and December 2013 with the diagnosis of glioma based on preoperative MRI after obtaining the appropriate informed consent. The manuscript has been revised for its publication by the Clinical Research Ethics Committee of Bellvitge University Hospital. Written informed consent was not considered necessary for the study, as it is an observational study based on our clinical practice. Data of the patients were anonymized for the purposes of this analysis. The confidential information of the patients was protected according to national normative.

All the patients presented a glioma in relation to the motor cortex, CST, or both based on preoperative work-up, which included standard anatomic MRI with gadolinium, functional MRI, and tractography of the CST.

Only patients with gliomas have been included in the analysis. Other patients operated with this technique of IONM and diagnosed with other tumors or vascular malformations have been excluded from the analysis with the aim of focusing our results in cases of infiltrative tumors.

Clinical Evaluation

Preoperative demographic and clinical data have been related with the outcome to establish clinical risk factors of postoperative deficit. Preoperative and postoperative motor function has been categorized according to the Medical Research Council Scale (MRCS) for muscle strength in 5 grades: grade 5, normal muscle contraction against resistance; grade 4, muscle strength is reduced but muscle contraction can move joint against resistance; grade 3, muscle strength is further reduced, so that the joint can be moved only against gravity; grade 2, muscle can move only if the resistance of gravity is removed; grade 1, only a trace or movement is seen or felt in the muscle or fasciculations are observed; grade 0, no movement is observed.
All the patients were operated on under general anesthesia using the monopolar train-of-5 stimulation technique for mapping and monitoring the CST during the resection (see below). Motor function of the patients was tested postoperatively and categorized with the MRCS motor score. In the case of postoperative paresis patients were followed-up until recovery. Motor deficits were considered irreversible after a 3-month period of follow-up. Patients were evaluated 3 months after the surgery for assessment of motor function and categorization of their performance status with the Karnofsky Performance Status (KPS) scale. New postoperative deficits were considered severe if the KPS of the patient was below 70 and mild/moderate if the KPS of the patient was ≥ 70. Intraoperative data were compared with the functional status of the patients at 3 months to establish prognostic intraoperative neurophysiological data of motor deterioration.

Anesthesia Considerations

All patients were operated on under general anesthesia using a total intravenous anesthesia regime with propofol and remifentanil to minimize the effect on the synapsis and therefore improve the neurophysiological studies during the surgery. Muscle relaxants were only used for orotracheal intubation.

Intraoperative Neuromonitoring

Multimodal intraoperatorive neuromonitoring was performed using the 32 channels ISIS system (Inomed Co., Emmendingen, Germany) equipped with a constant-current stimulator. Bilateral somatosensory evoked potentials from the median and posterior tibial nerve and MEPs by transcranial electrical stimulation and direct cortical stimulation were performed on all patients. In patients with tumors directly related or infiltrating the cortex, the motor strip was exposed and functionally mapped with a monopolar stimulator to find the hot spots of selective muscular activation for IONM during tumor resection. Previously and with the intention to limit the number of brain stimulations, the central sulcus was localized using the median nerve somatosensory evoked potentials phase-reversal technique with a strip electrode of 8 contacts (each 4 mm in diameter and with an interelectrode distance of 1 cm) placed perpendicularly to the assumed central sulcus.[1]

The same stimulation parameters were used for mapping and monitoring. A high frequency monopolar train-of-5 stimuli (500 msec duration each and 4 msec interstimulus interval) was applied at the cortical level. To minimize the risk of electrically induced intraoperative seizures the intensity of HFMS was never higher than 25 mA.[26]

In patients with tumors related to the CST but not with the motor cortex, such as insular gliomas, a subdural strip electrode was placed longitudinally all over the motor cortex with the aid of a neuronavigation system. Contacts of the electrode were tested to find the best cortical spot for IONM, usually at the hand area.

The target muscles to elicit MEPs were chosen by the neurosurgeon and the neurophysiologist depending on the location of the tumor.

Distal muscles of the upper and lower extremity were used for the registration of MEPs in all the cases (abductor policis brevis, extensor digitorum, adductor hallucis brevis, and tibialis anterior). Muscles in the hand area were used for the registration of the MEPs in the case of deep-seated tumors such as insular gliomas. For tumors located in the middle or distal third of the motor strip muscles of the face and the cricothyroid muscle were included. For tumors located in the proximal third of the motor strip proximal muscles (biceps, deltoid, quadriceps) were also included.

Resection of the tumor was performed under continuous monitoring of the CST with direct cortical stimulation (anodal stimulation) with a strip electrode combined with subcortical stimulation (cathodal stimulation) with a monopolar probe stimulator (Figure 1).

The inter-trial direct cortical stimulation rate was randomized to avoid electrical induced seizures.

An increment of ≥ 5 mA in the threshold to obtain the MEP, a persistent decrease in amplitude of the MEP > 50% and persistent MEP loss were considered intraoperative warning criteria.

After 1 of these phenomena occurred and accidental displacement of the strip electrode was ruled out, intraoperative measures to try to recover MEP responses were initiated. These measures included an increase in blood pressure, a transient halt of the resection at the point in which MEP changes occurred, irrigation of surgical bed with warm saline, and local papaverine instillation in the case of suspicion of vascular injury.

In these circumstances, if MEP responses returned to the baseline, surgical resection was carried on. If responses did not recover surgical resection was aborted.

Subcortical stimulation was initiated at high intensities (20 mA) and it was considered negative in cases of no-response at that intensity.

The intensity of the subcortical response per se was considered a warning criteria for stopping the surgery depending on the possibilities of complete resection of the tumor. In cases with low-intensity subcortical responses (5 mA or below) surgical resection was continued if a complete resection was judged as possible. In contrast, if the possibility of complete resection was not considered to be possible according to the preoperative image, intraoperative judgment, or neuronavigation, resection was stopped around 5 mA of subcortical stimulation.

Statistical Analysis

We performed 3 different analyses of the data. In the first analysis, using Logistic Regression (LR),[27] we wanted to select which data were statistically related with postoperative motor function. We recoded MRCS in 2 categories consisting in presence (M-) or absence (M+) of motor deterioration at 3 months. MEP response was also recoded in 2 categories. When there was no decrement or persistent decrease in amplitude of the MEP < 50%, it was recoded as MEP present (MEP+). If persistent decrease in amplitude of the MEP was > 50% or MEP was lost, it was recoded as MEP deterioration (MEP-). Secondly, we used the Rank Biserial Correlation Coefficient[28] to analyze the relation between subcortical stimulation intensity and the occurrence of motor deficit at 3 months, for the entire sample and for the subsample with subcortical stimulation ≤ 5 mA.

The third analysis was performed to explore a future objective criterion during surgery, based on the variables selected using LR and including different selected subcortical MEP thresholds. Assessment of decision-making can be performed using Receiver Operating Characteristic (ROC) curves.[29] The ROC curve is the result of plotting sensitivity, against the complement of specificity (1-specificity). The Area Under the Curve (AUC) given by the plot is an indicator of the accuracy of binary decision-making processes. We compared different diagnostic decision-making strategies to define a proposal for intraoperative management.

Analyses were performed using SPSS 21.0 (SPSS, Armonk, New York) and in-house code in MATLAB version 7.8.0 (The MathWorks Inc., Natick, Massachusetts).

RESULTS

Epidemiological and Clinical Data

Multimodal IONM protocol including cortical and subcortical mapping and monitoring with a monopolar train of stimuli was introduced in our center in November 2008. Between November 2008 and December 2013 a total of 115 patients were operated on with this technique. In the series, 92 patients were identified with gliomas, which are the patients included in the paper. The mean age of the patients was 47.29 years (17-73 years). Twenty-two patients (24%) presented with an irreversible motor deficit after 7 days of steroid treatment. Fourty-two patients (51.22%) were diagnosed with seizures exclusively. Five patients presented with a KPS score of 100 (5.43%), 35 with a KPS score of 90 (38.04%), 32 with a KPS score of 80 (34.8%), and 20 with a KPS score of 70 (21.7%).

Intraoperative Neurophysiological Data and its Relation With Persistent Motor Deficits

Significant intraoperative alterations in the MEPs were detected in 21 patients (22.8%): 12 patients (13%) with a persistent threshold increment ≥ 5 mA during the resection without significant decrease in MEP amplitude, 2 patients (2.2%) with a significant MEP amplitude reduction, and 7 patients (7.6%) with an MEP loss.

Subcortical stimulation was positive in 75 patients (81.5%) and negative in 17 patients (18.5%). Subcortical stimulation was ≥ 15 mA in 13 patients (14.13%), 10-14 mA in 18 patients (19.56%), 6-9 mA in 14 patients (15.2%), 4-5 mA in 19 patients (15.2%), and below 4 mA in 11 patients (12%). Seven patients presented a subcortical stimulation positive at 3 mA and 4 patients presented a subcortical stimulation positive at 2 mA.

Eighty-five patients were available for the analysis at 3 months (92.4%). Seven patients had to be excluded for the analysis. One patient with a postoperative hematoma and postoperative motor deficit, treated with surgical evacuation, 2 patients diagnosed with tumor progression and new motor deficits at 3 months (both patients with glioblastoma multiforme), and 4 patients that died because of tumor progression.

Fourteen patients presented a new motor deficit at 3 months (16.5%). Motor deficits were considered severe (KPS < 70) in 6 patients (7% of the series) and mild or moderate (KPS ≥ 70) in 8 patients (9.5 % of the series). Patients with a significant MEP threshold increment (≥ 5 mA) without significant amplitude decrement did not present with a deficit at 3 months. The 2 patients with significant MEP amplitude reduction presented new deficits. Six of the 7 patients with an MEP loss presented deficit at 3 months. The case with an MEP loss and no deficit has been qualified as a false positive case (see discussion). A data summary of the patients with significant MEP alterations and patients with persistent motor deficits is shown in Table 1

Postoperative Deficits Not Detected with the Technique

Out of the 14 patients with new motor deficits, 6 presented new deficits not detected intraoperatively (Table 1). One case was considered a false negative: a patient with an insular glioma and a postoperative deep-ischemic lesion in a perforating artery not detected intraoperatively. Five patients (5.9%) presented a deficit in non-monitored muscles (see discussion).

Intraoperative Seizures

Five patients presented intraoperative partial motor seizures (5.43%). Seizures were clinically and electrically resolved with cold saline irrigation. IONM with cortical stimulation was continued in 4 of these 5 patients. One patient presented a MEP loss after a seizure and surgical resection was stopped (see false positive case in the discussion).

Statistical Analysis

As previously mentioned we performed a forward stepwise LR analysis to identify which variables showed a significant association with persistent motor deficit at 3 months. Age, preoperative motor function, KPS score, and MEP response were the variables included as regressors in the analysis. After the estimation process the variables selected by the model were preoperative motor function and MEP response. Beta values, standard errors, significance of selected regressors, and general statistics about the model goodness-of-fit are represented in Table 2.

We found significant rank biserial correlations of subcortical MEP threshold with persistent motor deficit at 3 months, for the entire sample (R_{rb} = 0.4505, P < .01) and for the subsample with a subcortical MEP threshold ≤ 5 mA (R_{rb} = 0.5421, P < .01). The relation between the subcortical MEP threshold and the percentage of patients with persistent motor deficits is shown in Figure 2.

ROC curves were used to contrast 5 different simulated decision-making strategies. The first taking into consideration the combination of significant variables estimated with the previous LR analysis. In the other 4 models we added each one of the lowest subcortical MEP thresholds (5 mA, 4 mA, 3 mA, and 2 mA) to the previous variables following the same disjunction rule. Results achieved with ROC curves are presented in Table 3 for each 1 of the 5 different combinations. The values reported are AUC, significance (*P* - value), sensitivity, and specificity. Significance of the AUC tests the null hypothesis that the true AUC = 0.5 which means that the decision-making strategy is better than guessing.

The combination of preoperative motor function, MEP- Response, and subcortical MEP threshold of 3 mA or below yielded the best sensitivity and specificity for prediction of persistent motor deficit at 3 months.

This means that taking into consideration the subcortical MEP threshold, even as a sole criterion, may be helpful in reducing the incidence of false negative events, especially in patients that present with preoperative motor deficits (see Postoperative Deficits Not Detected With the Technique section in the discussion).

DISCUSSION

The monopolar train-of-5 stimulation technique has emerged in the recent years as a promising tool to assist the surgical resection of brain tumors.

The technique was first described and applied for the surgical resection of brain tumors under general anesthesia by Taniguchi et al in 1993.[16] Since then some papers have been published showing the usefulness of the technique for motor cortical mapping,[17-19] motor subcortical mapping,[4,7,21-24,30,31] and intraoperative neuromonitoring[1,2,4,5,6,22,30] with a low incidence of intraoperative seizures.

The criteria used as intraoperative warning signs and the data associated with irreversible motor deficit are quite variable among the authors.[26]

It seems to be general agreement that an MEP loss during the resection reflects an intraoperative injury to the CST and, therefore a postoperative motor deficit is expected with a high probability.

The incidence of a motor deficit after an irreversible MEP loss varies between 80% and 100% among authors.

Cedzich et al[1] report an incidence of motor deficit of 100% in cases of MEP loss. Half of their patients with reversible MEP loss during the resection also presented minor deficits after the surgery.

We must mention that in our series we have not observed a reversible MEP loss, so that in every patient where an MEP loss occurred it was not recovered after the appropriate measures described in the methodology were applied.

In the paper published by Kombos et al,[2] an irreversible MEP loss and a decrease in amplitude superior to 80% were the factors associated with postoperative permanent deficit. A latency prolongation of > 10% has been associated with a postoperative deficit by the same authors.

We have found latency prolongation a very difficult parameter to assess during the resection, as a lot of variation can be observed due to anesthetics. For this reason this parameter has not been evaluated in our series or in other papers.[1,4,5]

Neuloh et al,[5] in one of the largest series of tumors operated with this technique, observed significant changes in the MEPs during resection in 39% of 177 patients. Eighty percent of the patients with an MEP loss presented a motor deficit whereas 25% of the patients with an irreversible MEP amplitude reduction superior to 50% presented a motor deficit. In contrast, reversible MEP losses or reductions in MEP amplitude presented a low incidence of motor deterioration (4.5% and 6.25% respectively)

Seidel et al[4] demonstrated a 75% probability of neurological deficit in cases of intraoperative MEP loss.

In our series we have observed a motor deficit after an intraoperative MEP loss in all but one case (85% risk of permanent motor deficit in cases of MEP loss).

The patient was a 35-year-old woman with a right-sided temporo-insular glioma. During the surgery, the patient presented with a stimulation-induced partial motor seizure. After its recovery, IONM with cortico-subcortical stimulation was started again and a few minutes after obtaining positive cortical responses, MEPs were lost and did not recover so surgery was stopped at that point. The patient awakened without motor deficits. MEP loss in this case was probably a result of a failed response due to the previous seizures. This can be classified as a false positive case. In this situation, intraoperative electrocorticography during stimulation could have detected this phenomenon. False positives, however, occurred in only 1 patient (1.08%). The incidence of intraoperative seizures can be considered very low in our series (5.26%) and comparable to the incidence reported by other authors using the same technique.[22]

Significant alterations in intraoperative MEP responses have also been associated with a motor deficit in our series.

We have found a good correlation between significant decrease of MEP amplitude (> 50%) and postoperative deficit in 2 patients (100% deficit). As mentioned before, some authors have found an incidence of motor deficits between 50-80% in cases of significant MEP amplitude reduction during the resection.[5,18]

In our series, 12 patients presented a threshold increment ≥ 5 mA for cortical MEPs with an MEP amplitude reduction of less than 50% at the end of the surgery. These patients presented with no permanent deficits.

The criteria based on threshold increment has been proposed for several types of monitoring. The theoretical basis is that the largest corticospinal axons have lowest threshold and greatest susceptibility to damage so that threshold elevation should provide highest sensivity.[32]

Following this reasoning, authors such as Szelenyi et al[25] and Seidel et al[17] have considered threshold higher than 2 mA[25] and 5 mA[17] as a warning criteria in supratentorial surgery.

However, there are some technical critiques that could undermine threshold tracking. Threshold exhibits some variability depending on anesthesia depth and on the studied muscle. Also, fade can gradually increase threshold.

In our series, patients with a persistent threshold increment ≥ 5 mA for cortical MEPs without significant MEP amplitude reduction presented no postoperative deficits at 3 months.

Postoperative Deficits Not Detected With the Technique

Six patients presented with a postoperative persistent new deficit at 3 months not detected intraoperatively.

One of the patients was diagnosed with an insular glioma and presented a postoperative hemiparesis due to a perforating artery infarction seen on postoperative MRI which was not intraoperatively detected. Although the infarction must be associated with an intraoperative event we cannot exclude the possibility of postoperative vasospasm as a possible cause of the deficit.

Five patients also presented a deficit that was not intraoperatively detected by the cortical MEPs. All presented a common feature, which is the location of the glioma above the corona radiata and infiltration of the motor strip in its proximal aspect (between the hand area and the midline). This is usually a critical region in terms of function since all the proximal muscles of superior and inferior limbs are included in the proximal third of the motor strip (ie, in the motor strip between the superior frontal sulcus and the midline).

Out of the 5 patients, 3 presented deficit in proximal muscles of upper and lower limbs. These were 3 of the first 10 patients operated on with the technique in our series. Initially we did not include proximal muscles for the registration of the MEPs (according to IONM technique described by Taniguchi[16]). After the preliminary analysis, we have included proximal muscles for the registration of the MEPs but, despite this modification, we have also detected 2 additional cases.

One patient presented an upper limb deficit (3/5) after a resection of the glioma. Cortical MEPs at the hand area were normal and subcortical stimulation was positive at 2 mA. One patient presented a deficit in finger extension and cortical MEP recorded at the thenar region was stable during the resection. Subcortical MEP threshold at the end of the resection was 3 mA.

The explanation for this can be that for tumors located above the corona radiata, postoperative deficits occult to the IONM strategy can occur if the appropriate muscles for the registration of the MEPs are not selected accurately, especially when positive subcortical responses are obtained at low intensities.

This raises the question of how many muscles should be included for the registration of the cortical MEPs in tumors infiltrating the motor cortex area, where the fibers of the pyramidal tract are very loose and distributed in a fan-shaped fashion. In tumors of this location very selective deficits may occur, sometimes occult to the IONM strategy.

This phenomenon of deficit in non-monitored muscles is only described by Neuloh et al.[5] In this paper authors report a deficit in non-monitored muscles in 3.1% of the patients. In the rest of the papers analyzed this phenomenon either did not occur or is not specifically mentioned. We have not observed this phenomenon in deep-seated tumors, such as tumors below the corona radiata and insular gliomas. In these locations motor fibers converge tightly, and probably, as is argued by Neuloh et al,[6] responses obtained in the upper extremity muscles appear to be representative of all deep motor fibers.

Subcortical Intensity

Nowadays intraoperative subcortical stimulation can be considered the gold standard method for identification and preservation of the CST during glioma resection. In this sense, 1 of the major advantages of using this type of stimulation at the subcortical level is that its positivity depends on the intensity used and correlates with the distance to the CST.[21,23,24,31,33] Using high intensities of subcortical stimulation (ie 20 mA) a positive response can be obtained even if the CST is located far away from the resection cavity. As the resection advances, intensity needed to elicit subcortical MEPs decreases progressively. This offers the possibility of having intraoperative feedback of the working-distance to the CST as the tumor resection advances.

Subcortical stimulation in our series was positive in 75 patients (81.5%) and negative in 17 patients (18.5%) after the application of a subcortical stimulation with an intensity up to 20 mA. In these 17 cases the CST was considered further away from the resection cavity than it was supposed to be according to the preoperative data.

It is proposed that there is a linear relation of 1 mA per 1 mm of brain tissue. [7,24] This relation, however, has also demonstrated to be non-strictly linear by some authors[23,34] and it may also depend on some factors such as age, tumor infiltration, or edema.

There is also general agreement in the literature that to prevent subcortical damage to the CST, surgical resection should be done until reaching a safe-distance margin to the CST.

Sala et al[22] does not recommend removing tissue with positive subcortical stimulation below 5-7 mA using the monopolar train-of-5 stimulation technique.

Kamada et al[23] argue that surgical manipulation within 10 mm to the CST may lead to ischemic risks in eloquent fibers.

Prabhu et al[24] demonstrated a high risk of neurological deterioration in patients with a subcortical stimulation threshold ≤ 5 mA. This intensity corresponded to a distance ≤ 4 mm to the CST based on tractography. In the same study, patients with a minimum subcortical stimulation threshold ≥ 10 mA did not develop neurological deficit. The measured distances to the CST in this group were ≥ 6 mm.

Nossek et al[7] demonstrated no permanent motor deficits in patients with positive subcortical stimulation ≥ 7 mA. In contrast patients with subcortical stimulation with a threshold < 3 mA presented a high probability of neurological deterioration.

Seidel et al[4] reported the possibility of performing tumor resections without causing neurological deficits reaching a subcortical stimulation threshold of 1 mA. The paper does not include patients with tumors infiltrating the primary motor cortex.

Our recommendation based on our intraoperative data is to stop the resection before reaching a subcortical MEP threshold of 3 mA. Below that threshold the probability of having an MEP loss, and in consequence, a new motor deficit, is high. We have observed, in our series, that MEP losses sometimes occur suddenly and in relation with low subcortical intensities.

According to our results we can not recommend proceeding with the surgical resection after obtaining a positive subcortical ≤ 3 mA especially in 2 types of patients: patients with preoperative motor deficits and patients with tumors infiltrating the motor cortex or the most proximal aspect of the CST where the fibers of the tract are less compact and selective deficits of muscles not included in the IONM strategy can occur.

Limitations

We want to point out that, due to the size of the data set, our results can lead to over-optimism.[35] The best solution would be to validate our results with an external sample not used to define the decision rule, with a replication of the same procedures that we have used in our study. We consider this fact an important limitation of our study.

Szelény et al,[21] in 2011, published the first paper comparing the ability of different types of subcortical stimulation in the same patient group for localization and preservation of the CST. The authors showed a good correlation of the positivity of subcortical responses with the bipolar 50 Hz technique and the monopolar train-of-5 technique at intensities below 10 mA. The correlation is good, even at intensities that are not considered critical with the monopolar train-of-5 stimulation technique. This raises the question of which technique is optimal, at least at the subcortical level, to achieve a maximal tumor resection. Further studies comparing different techniques of subcortical stimulation in the same group of patients are needed to answer this question.

CONCLUSIONS

The HFMS can be considered a useful technique for the assistance of glioma resection in patients with tumors related with the motor cortex and the CST. Significant MEP amplitude reduction or MEP loss during tumor resection is associated with a high probability of persistent motor deficit.

There is a statistically significant association between the threshold of positive subcortical stimulation and the risk of motor deterioration, supporting the evidence of previous studies that, with this type of stimulation there is a relation between the intensity and the distance to the CST. According to our data analysis, we have found it recommendable to stop the resection of a tumor before obtaining a subcortical MEP threshold of 3 mA, particularly in patients with preoperative motor deficits. Appropiate selection of muscles for the registration of the MEP is mandatory, in order to avoid deficits in non-monitored muscles, especially in patients with tumors located above the corona radiata.

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Figure 1. Intraoperative image shows the placement of a strip electrode over the motor cortex to elicit the cortical MEPs. A monopolar probe is also used to elicit subcortical MEPs as tumor resection advances.

Figure 2. Subcortical MEP threshold (horizontal values) and its relation with the percentage of patients with postoperative motor deficit.

Figure 1

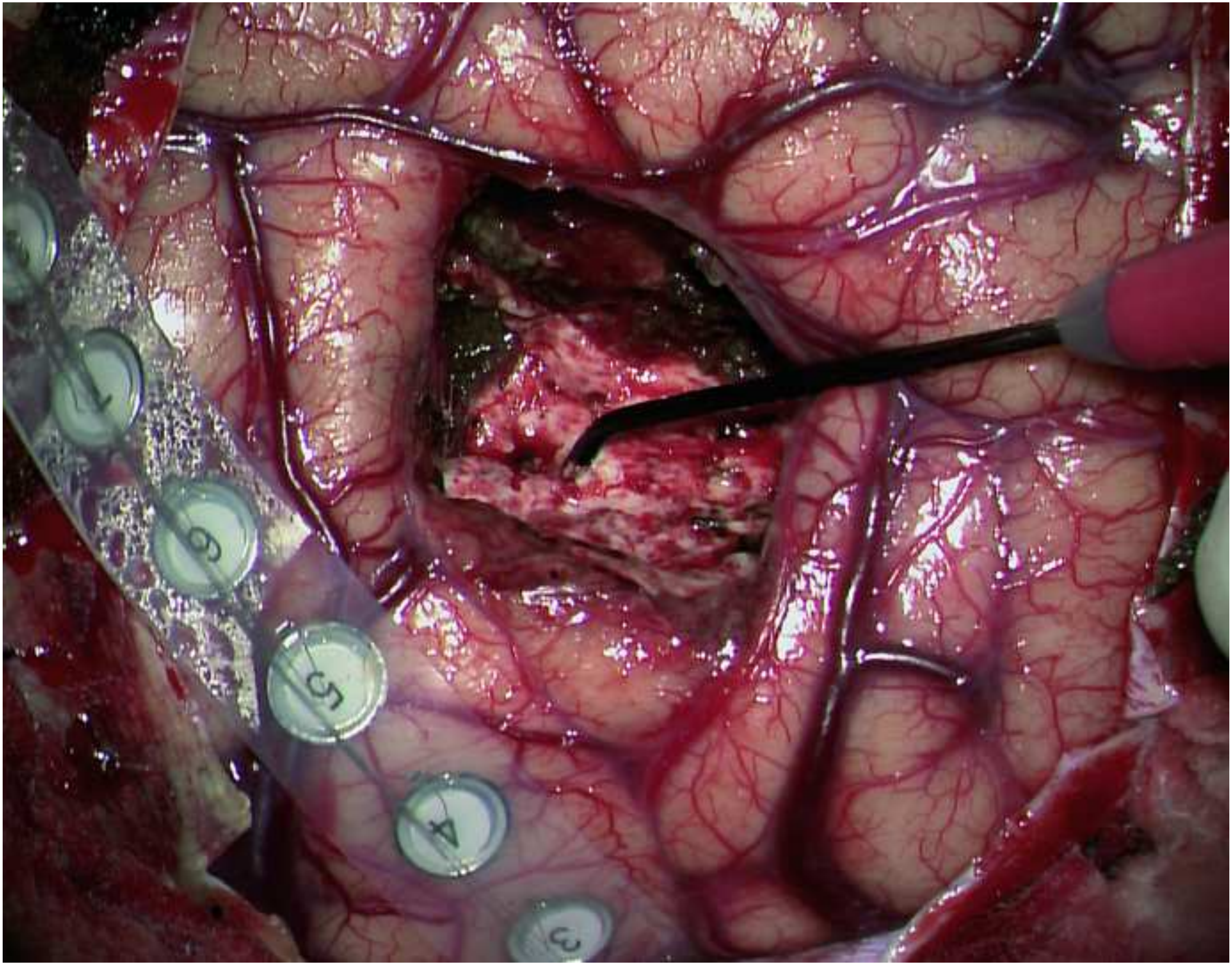

Figure 2

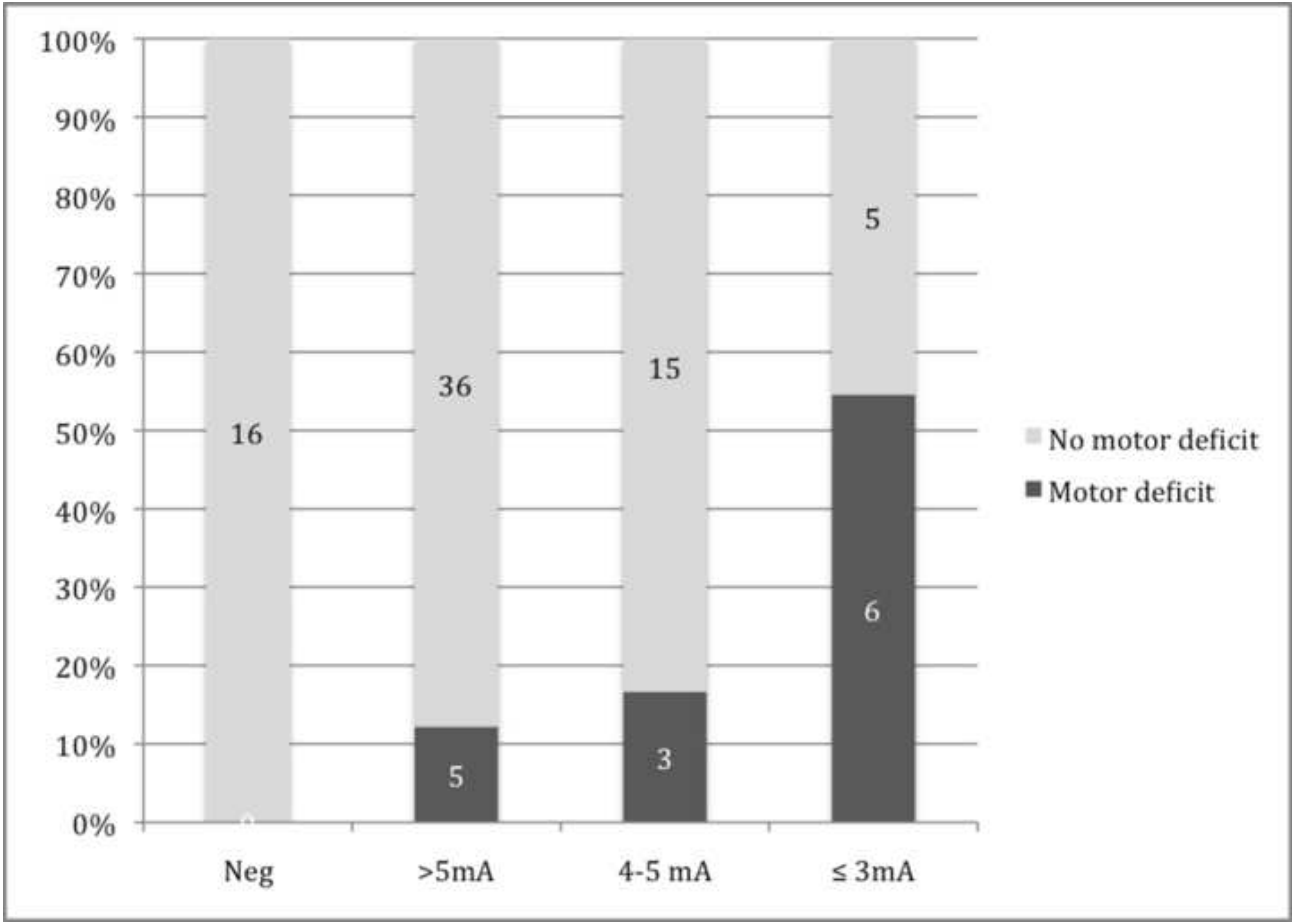
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
16
36
5
15
3
5
6
No motor deficit
Motor deficit
Neg
>5mA
4-5 mA
≤ 3mA

Table 1

Patient number	Age (y)	Tm	Loc	MEP status	SC MEP (mA)	Motor preop	Motor postop	Motor 3 m	KPS pre	KPS 3 m
2	40	AA	Motor R	Det	15	4+hand	1 hand	3 hand	70	70
69	33	AO	Frontal premotor L	Det	3	5	2 sl	4 sl	90	90
12	54	GBM	Motor R	Lost	5	3 foot	0 foot	0 foot	80	80
13	49	AA	Postrol R	Lost	5	5	0 hand	1 hand	90	80
38	67	GBM	Frontal subcort R	Lost	5	4 hemi	0 hemi	1 hemi	70	60
47	35	GBM	Insula	Lost	12	4 hemi	4 hemi	4 hemi	70	70
58	43	LGG	Temporal and insula L	Lost	2	5	0 hemi	1 hemi	90	60
82	42	AA	Insula R	Lost	2	5	0 hemi	2 hemi	80	60
90	24	AA	Motor R	Lost	2	4 hand	0 hand	2 hand	80	70
6	41	AA	Frontal premotor L	TH	20	4+ sl	1 hemi *	4+ sl	80	80
9	51	AA	Parietal R	TH	Neg	5	5	5	80	80
11	42	AA	Frontal R	TH	Neg	5	5	5	80	80
18	29	AA	Parietal L	TH	15	4 hemi	4 hemi	4 hemi	80	80
20	34	AA	Frontal and insula R	TH	8	4 sl	4sl	4sl	80	90
22	53	GBM	Temporal and insula R	TH	9	5	5	5	80	90
23	43	GBM	Parietal R	TH	6	5	5	5	90	90
25	59	GBM	Frontal L	TH	10	5	5	5	90	100
26	50	AA	Frontal premotor L	TH	20	5	2 hemi *	5	100	80
27	28	LGG	Frontal and insular R	TH	Neg	5	5	5	80	90
54	33	AA	Postrol R	TH	5	4 il	3il	4il	90	90
62	55	GBM	Frontal premotor R	TH	4	5	4sl	5	90	90
5	55	GBM	Frontal premotor R	N	10	4 il	0 hemi	3 hemi	70	60
7	68	LGG	Frontal premotor L	N	15	4il	0 hemi*	2 hemi	70	50
10	30	LGG	Postrol R	N	15	5	3 il	4 il	90	70
31	31	LGG	Insula L	N	20	0 hemi	0hemi	1hemi	100	60
67	64	GBM	Motor R	N tenar	3	5	4 finger ext	4 finger ext	100	90
91	56	GBM	Motor R	N tenar	2	5-sl	2 sl	3sl	80	70

Table 1 Data of the patients with significant intraoperative MEP changes and patients with persistent motor deficit at 3 months.
y: years; Tm: tumor diagnosis; Loc: anatomical location of the tumor; MEP status: motor evoked potential status; SC MEP: subcortical motor evoked potential measured in mA at the end of the resection; Motor preop: preoperative motor status measured with the MRCS (see text); Motor postop: motor status in the inmediate postoperative period (first 24h); Motor 3m: Motor status at 3 months; KPS pre: Preoperative Karnofsky performance scale; KPS 3m: Karnofsky performance scale at 3 months; AA: anaplastic astrocytoma; AO: anaplastic oligodendroglioma; GBM: glioblastoma multiforme; LGG: low grade glioma; R: right; L: left; Postrol: post-rolandic; Det: deterioration (see text); TH: threshold increment (see text); hemi: hemiparesis; sl: superior limb; il: inferior limb; ext: extension; *supplementary motor area syndrome
Note: patients with deficit at 3 months are highlighted in grey

Table 2: Model goodness-of-fit and regressors significance of Logistic Regression

Model Goodness-of-fit	**R^2 Cox & Snell**	**R^2 Nagelkerke**	**X^2**	***P* - value**
	0.304	0.501	30.79	$P < .001$
Regressors	**B**	**SE**	***P* - value**	
PMF	1.755	0.799	$P = .028$	
MEP Response	4.155	1.177	$P < .001$	

R^2: Coefficient of determination, X^2: Chi-square, B: Coefficient for the predictor, SE: Standard error of the coefficient for the predictor, PMF: Preoperative motor function, MEP: Motor evoked potential.

Table 3: Receiver Operating Characteristic curves results and significance for the different decision making strategies.

Decision-making strategy	**AUC**	**p-value**	**Sensitivity**	**Specificity**
PMF or MEP Response	0.836	*P* < .001	0.8	0.871
PMF or MEP Response or ≤ 5 mA	0.748	*P* = .003	0.867	0.629
PMF or MEP Response or ≤ 4 mA	0.826	*P* < .001	0.867	0.786
PMF or MEP Response or ≤ 3 mA	0.855	*P* < .001	0.867	0.843
PMF or MEP Response or ≤ 2 mA	0.836	*P* < .001	0.8	0.871

PMF: Preoperative motor function, MEP: Motor evoked potential, AUC: Area under the curve.