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TITOLO DELLA TESI DI DOTTORATO

La neurofisiologia intraoperatoria della corteccia motoria e dei fasci cortico spinali: vantaggi, limiti e prospettive future.

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Intraoperative neurophysiology of the motor cortex and cortico spinal tracts: advantages, limits and future perspectives.

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ABSTRACT

Background. Brain surgery in motor areas requires a balance between radical surgical resection and risk of postoperative motor deficits. Intraoperative neurophysiological monitoring, especially with motor evoked potentials (MEPs), provides a valuable help in such conditions; however, the correlation between MEP amplitude changes and clinical outcome is not always clear. A stronger neurophysiological predictor of outcome is therefore desirable.

Objectives. The aims of this Thesis are: a. to analyze the limits of MEP monitoring during brain surgery in motor areas with a special attention to the confounding factors that may alter the interpretation of MEP changes during surgery; b. to verify and confirm the role of a strong neurophysiological predictor of outcome - the D-wave monitoring - during surgery for intramedullary spinal cord tumor; c. to apply the D-wave monitoring during brain surgery in motor areas. The Thesis is divided in three sections according to the aforementioned objectives.

Materials and Methods. In the first section, a consecutive cohort of 157 patients submitted to surgical removal of a tumour adjacent to the motor areas and CST with simultaneous subcortical motor mapping and DCS MEP monitoring were analysed. Motor function was assessed the day after surgery, at discharge, and at further follow-up postoperatively. A post-hoc analysis was conducted in order to analyse possible pre- and postoperative confounding factors during MEP changes interpretation. In the second section, a consecutive cohort of 219 patients submitted to surgery for intramedullary spinal cord tumors (ISCTs) with simultaneous muscle MEP and D-wave monitoring were analysed. Motor function was assessed the day after surgery, at discharge, and at further follow-up postoperatively. A post-hoc analysis was performed in order to verify the reliability of D-wave monitoring as a strong outcome predictor. In the third section, we report the experience of 3 consecutive cases operated on for brain tumors in motor areas with the aid of D-wave monitoring.

Results. Section I: the location of the tumour in the prefrontal cortex and along the CST are related with a higher rate of postoperative motor deficits (p=0.04 and p=0.008, respectively); for tumours located in the prefrontal cortex, 53% of patients showed new motor deficit with changes of MEP in 16% of them. Different muscles showed different capability to predict new motor deficits; furthermore, the higher is the number of muscles with MEP amplitude below the threshold, the higher is the probability of a new stable motor deficit. Section II: D-wave monitoring is a valuable help during surgery for ISCTs and show a sensitivity of 33.3%, a specificity of 99.2%; positive predictive value is 50% and negative predictive value is 98.4%. The accuracy calculated is 97.6%. Section III: we were able to record TES D-wave in patients 2 and 3; in patient 1 we obtained the D-wave only with TES of the hemisphere contralateral to the tumour. It was not possible to obtain a clear D-wave from DCS in all three patients. In patients 2 and 3 it was possible to obtain the D-wave through subcortical bipolar stimulation along CST.

Conclusions. Intraoperative neurophysiology is a valuable help during surgery in motor areas. MEP monitoring provide useful and reliable information during surgery, but it is not always easy to analyse the relationship between intraoperative changes and clinical outcome. D-wave monitoring is a well-known technique and our results confirmed its role of strong outcome predictor. The application of this technique for brain surgery can help to overcome the limits of MEP monitoring alone.

INDEX

Introduction

Surgical removal of tumors located in or nearby the motor areas is classically complicated by a dichotomy: the need for a maximal resection in order to achieve a good overall survival[1,40,52] and the need for absent or at least minimal new postoperative motor deficits. It is particularly difficult to balance between these two factors: in fact, on one side a maximal resection of the tumor can affect the prognosis of the patients[51,61], but at the same time it can damage the quality of life after surgery with the onset of new postoperative deficits.

Despite recent technological advances like diffusion tensor imaging (DTI) fiber tracking[14,62] and neuronavigation[45], intraoperative neurophysiological monitoring (IOM) remains the gold standard technique which helps the surgeon to localize the eloquent areas and at the same time it produces real time data regarding the functional status of the cortex and the subcortical fibers[36-38,46,49]. Intraoperative monitoring of somatosensory evoked potentials (SSEPs) during surgery was the first application of IOM in critically eloquent areas; however, the theoretical assumption that a damage of somatosensory pathways could predict a motor pathways damage due to their anatomical proximity produced a high rate of false negative results after surgery, meaning significant postoperative motor deficit without SSEPs changes[39,48,49]. However, from a neurophysiological standpoint, we should not consider these as false negative results because we should not expect SSEPs to predict motor injury. In order to overcome this misleading limit, the introduction of motor evoked potentials (MEPs) monitoring gained increasing attention as a reliable tool able to identify critical surgical steps during surgery in the motor areas and nearby the corticospinal tract (CST). Surgery nearby M1 can cause multiple types of MEPs changes but an unambiguous relationship between intraoperative MEPs changes and clinical outcome can be drawn in only one condition, that is the irreversible loss of evoked potentials. In this condition, a stable new neurological deficit is expected. Irreversible deterioration is an intermediate change of the evoked potential and its interpretation is not always straightforward. Many authors evaluated the deterioration of MEPs during surgery [29,30,36,41,56] in order to understand how relevant should be the reduction of the amplitude to create a stable motor deficit. According to this, two deterioration thresholds have been proposed: amplitude reduction below 50% and below 80% of the initial value. However, the evaluation of these two thresholds might be further complicated by other factors like the number of muscles with a relevant deterioration of amplitude and the different types of muscles that might express significant changes in MEPS amplitude.

The aforementioned MEPs and SSEPs monitoring techniques have been extensively adopted also during intramedullary spinal cord tumors (ISCTs). Recording of an evoked potential after stimulation of M1 transcranially can be done at two levels: proximal (along the spinal cord) and distal (muscle MEPs). The former, namely the D-wave, represents the "direct" expression of the pyramidal cell stimulation and it is characterized by a very short interval between central stimulus and EP recordings along the spinal cord (depending on the level of recordings along the spinal cord). The D-wave is known as a strong predictor of clinical outcome during surgery for ISCTs: the preservation of the D-wave amplitude above 50% of the baseline value during surgery is related with a very low risk for new and stable neurological deficits[6,28,50].

Due to the relevant clinical value of D-wave monitoring during ISCTs, a few Japanese clinical reports evaluated the role of D-wave during brain surgery nearby M1[11,12,60], in order to overcome the uncertain clinical value of intermediate MEPs changes. However, the application of D-wave monitoring for brain surgeries requires the percutaneous positioning of an epidural electrode at a high cervical level (C2-C3). Being this point the main limitation of the procedure, D-wave monitoring is not scheduled in the routine IOM setting for surgery around M1 in most countries. It should be mentioned, after all, that routine procedures of neuromodulation surgeries require percutaneous positioning of epidural electrode possibly reducing the rate of surgical risk related to the electrode positioning.

This thesis is aimed to address the following hypotheses: 1. Different modalities of IOM setting during surgery in motor areas might influence the final reliability of IOM; 2. D-wave monitoring during intramedullary spinal cord tumors (ISCTs) surgery is a strong predictor of long term postoperative motor deficit; 3. The application of D-wave monitoring during surgery in motor areas might help to overcome the limits of conventional muscle MEPs monitoring especially in the aforementioned conditions in which intermediate changes of MEPs amplitude cannot permit a clear relationship between intraoperative neurophysiology and clinical outcome.

The analysis of these hypotheses will be separately addressed in the different section of the thesis: starting from the limits of conventional IONM techniques during surgery in motor areas, we will attempt to define which kind confounding factor can alter the final reliability of MEPs monitoring and how they can produce misleading results in order to underline the need for stronger and straightforward outcome predictors (Section 1). D-wave monitoring is known to be a strong predictor of outcome but its current application is limited to spinal cord surgery; we will analyze the efficiency of D-wave monitoring during ISCTs surgery in order to confirm its role of strong outcome predictor (Section 2). In the conclusive section of the thesis we will apply D-wave monitoring to brain surgery in motor areas in order to overcome the uncertainties of muscle MEPs monitoring (Section 3).

SECTION 1: MUSCLE MEPs MONITORING DURING BRAIN SURGERY IN MOTOR AREAS: LIMITS AND PERSPECTIVES.

Background

Brain surgery around M1 has been strongly related to IOM due to the possibility to tailor the surgical strategy in order to maximize the resection and reduce the risk of neurological sequelae. The standard neurophysiological approach to such tumors is bimodal and based on afferent pathways (SSEPs) and efferent pathways (MEPs) monitoring. As previously mentioned the role of SSEPs has been overcome by MEPs due to their capability to investigate directly the motor pathways instead of the indirect data provided by SSEPs.

The interpretation of MEPs changes during surgery is not always clear. A stable EP reassure the surgeon about the neurological integrity of the patient and encourages him to pursue a more extensive tumor resection; on the other hand, an EP loss stops the surgeon and defines a high risk for new motor deficit. These two conditions have a clear relationship with the outcome[56]. However, intermediate changes of the EPs can complicate the intraoperative management of patients due to uncertainties of their clinical value. Furthermore, the application and settings of IOM can be influenced by multiple technical factors such as the number and the type of muscles available for recordings.

In this section, we reviewed our experience in IOM assisted surgery in motor areas in order to analyze the influence of different muscles sensitivity and specificity on final positive predictive value (PPV) of IONM. We hypothesized that the difference in the number of muscles with MEPs deterioration has a significant influence on the final interpretation of IOM; moreover, different muscles have different weight on the final positive predictive value (PPV) of IOM.

Methods

Patients population

From January 2012 to December 2016 at the Neurosurgical Institute of Verona, 157 patients (91 males) with a mean age of 51 years (range 11–80) were submitted to surgery for brain lesions involving or adjacent to the cortical and/or subcortical motor areas and pathways with the aid of direct cortical stimulation (DCS) muscle MEPs monitoring. All patients of the study had at least 3 months of follow-up. There were 3 pediatric patients (age < 18 years).

Neurological and radiological assessment

Preoperatively, every patient underwent a physical examination according to the Medical Research Council (MRC) scale[4](table 1.1): six different skeletal movements (arm flexion, hand extension, thumb abduction, leg flexion, dorsiflexion of the foot and of the big toe) were evaluated and graded (grade 0 to 5 of the MRC scale).

Table 1.1. Muscle strength assessment according to the MRC scale

MRC grade	*Muscle strength*
0	Absent muscle contraction
1	Contraction, no active movement
2	Active movement that cannot overcome gravity
3	Active movement that can overcome gravity
4	Active movement against gravity and resistance
5	Normal muscle strenght

MRC=Medical research council

Their preoperative motor deficits were none (94), mild (35), moderate (25), or severe (3). The mean interval between the clinical onset of symptoms and the diagnosis was 8.4 months. Their main clinical presentations were seizure (80), paresis (32), asymptomatic MRI tumor progression (20), dysphasia (8), altered mental status (6), headache (5), visual disturbances (3), paresthesia (2), or gait disturbances (1). Over half (86) were on maintenance anticonvulsant therapy.

All patients underwent MRI for diagnosis and localization of the tumor; DTI fiber tracking of the CST was collected whenever possible; the data collected were used for intraoperative neuro-navigation (Stealthstation Surgical Navigation System, Medtronic, USA). Tumor locations were anterior to the primary motor gyrus - M1 - (34), deep frontotemporal extending to the insula (32), M1 (26), primary somatosensory gyrus - S1 - (22), subcortical near the CST (19), deep temporoparietal (13), or M1 and S1 (11). Left–right hemispheric distribution was approximately equal.

All patients underwent postoperative CT scan and/or MRI in order to evaluate the presence of surgical complications (secondary hemorrhage, increasing edema and ischemia) and the grade of surgical resection. The degree of resection was classified as radical, near radical and partial according to CT or MRI contrast-enhanced images obtained within 48h after surgical procedures. All the cerebral lesions were classified on the basis of histopathological findings according to WHO 2007 classification[31].

A radical removal was obtained in 72.6% of cases. The lesions were glioblastoma (68), anaplastic astrocytoma (37), low-grade glioma (18), metastatic (11), meningioma (7), cavernoma (10), or other tumors (6).

The motor status was routinely assessed immediately after surgery, 24 hours after surgery, at discharge (on average 8 days after surgery, with a range between 3 and 20 days), and at follow-up. Any new surgery-related motor deficit was differentiated in temporary and permanent. A temporary deficit was defined as a new or aggravated postoperative motor deficit that disappeared during the follow-up period. A new permanent deficit was defined as a new or aggravated motor deficit related to surgery, which did not resolve to the preoperative status during the follow-up period. The motor function - as an average of the scores of all muscles - was considered preserved or mildly compromised when the mean value of strength was $\geq$ 4 MRC grade; moderately compromised when it was between 2 and 4 MRC grades; severely compromised when it was $<$ 2 MRC grade. Furthermore, the difference between postoperative and preoperative evaluations was classified as follows: no new paresis; new mild paresis (if mean MRC value decreased less than 1 grade compared to the preoperative value); new moderate paresis (if mean MRC value decreased between 1 and 2 grades); new severe paresis (if mean MRC value decreased more than 2 grades) (table 1.2).

Table 1.2. Classification of clinical outcome according to the variation of preoperative MRC scale.

Clinical definition	*Clinical characteristics*
no paresis	no changes between post-op and pre-op
transient paresis	only temp. change of mean MRC g. value
persistent mild paresis	mean MRC g. follow up - mean MRC g. pre-op between 0 and -1
persistent moderate paresis	mean MRC g. follow up - mean MRC g. pre-op between -1 and -2
persistent severe paresis	mean MRC g. follow up - mean MRC g. pre-op inferior to -2

MRC=Medical research council

Anesthesia protocol

The anesthesia protocol applied was a total intravenous anesthesia (TIVA) obtained by a continued infusion of Propofol (100-150 μg/kg/min) and Fentanyl (1μg/kg/min), avoiding bolus. Short acting relaxants were administered for intubation purpose only and then avoided. Halogenated anesthetic agents and nitrous oxide were avoided.

Intraoperative monitoring and warning criteria

Muscle evoked potentials were initially elicited by transcranial electrical stimulation (TES) via corkscrew needle electrodes from the scalp. Short trains of 5 to 7 square-wave stimuli of 0.5 ms duration and interstimulus interval of 4 ms were applied at a repetition rate up to 2 Hz through electrodes placed at C1 and C2 scalp sites, according to the 10/10 EEG system with maximum intensities of 200mA. Muscle responses were recorded via needle electrodes inserted in contralateral upper and lower extremity muscles (abductor pollicis brevis, extensor digitorum longus, and biceps brachialis for the arm and tibialis anterior and abductor hallucis for the leg) and if the facial nerve integrity was at risk, we recorded the potentials via needles inserted in contralateral orbicularis oculi and orbicularis ori muscles. The Axon Sentinel-4 evoked potential system with modified software (AXON System, Inc., Hauppage, NY) and more recently the Inomed ISIS INM System (Inomed, Medizintechnik GmbH, Emmendingen, Germany) were used for stimulation and recording. Once the dura mater was opened, if M1 was accessible, the central sulcus was identified using the median nerve somatosensory evoked potentials (SSEPs) phase-reversal technique, recording from a strip electrode[3]. Then, the same cortical electrodes were used as an anode for DCS of the motor cortex, while cathode was at Fz. The electrode with the lower threshold to elicit contralateral MEPs was then used for monitoring MEPs using the same parameters as for TES, except for much lower intensity (up to 35mA). TES was used before opening the dura mater, whereas DCS was used whenever possible. Before the beginning of surgery, the baseline MEPs values were recorded with TES technique once the patient was positioned then it was verified during the dural opening. Once the surface electrode was positioned and before starting the tumor dissection, the lower threshold to elicit contralateral MEPs was set as baseline value for DCS MEPs.

MEPs were sequentially recorded and observed by a technologist trained in IOM techniques. An experienced neurophysiologist provided supervision and interpretation of IOM data, that were analyzed in real time and monitored for amplitude and latency. Depending on the status of the resection, intervals were shortened to guarantee maximum safety. MEPs amplitude was evaluated by measuring peak to peak differences, whereas latency was defined as the span between the start of the stimulation in a given sequence and the first assessable amplitude. The surgical removal of the tumor was obtained with the aid of an ultrasound aspirator and neuronavigation. In case of MEPs amplitude reductions during surgery, technical issues were ruled out at first, then systemic blood pressure, anesthesia and body temperature were checked. If the reduction was still present, two alert levels were used: the first one was a persistent decrease in MEPs amplitude or an increase of the threshold to elicit MEPs and the second one was a loss of MEPs. According to the aforementioned levels of alarm, a significant deterioration of the amplitude was always reported to the surgeon; the second level was always followed by a modification of the surgical strategy that included temporary halt of resection, readjustment of retractors, warm irrigation, irrigation with Papaverine to avoid vasospasm and increasing of systemic arterial blood pressure. Depending on the recovering of MEPs and the preoperative planning, surgery was resumed or aborted.

Muscle MEPs changes comprehended reversible (reduction and loss) and irreversible changes (reduction and loss). Irreversible reduction of amplitude defined a persistent reduction of the muscle MEPs amplitude (but still present at the end of the procedure) that did not recover despite all the aforementioned anesthesiological and surgical rescue steps. Irreversible loss defined the complete and persistent disappearance of the muscle MEPs despite all the rescue manoeuvres. Due to the retrospective nature of the present study it was not possible to evaluate separately the reversible variation of the muscle MEPs, thus the comparison between clinical outcome and muscle MEPs changes were plotted in 2 x 2 tables.

Statistical analysis

Different coefficients were used to estimate the correlation between MEPs and postoperative clinical outcome (MRC scale). Muscle MEPs changes were evaluated in a post hoc fashion and the results were plotted categorizing the clinical outcome and muscle MEPs changes in two groups each: stable vs neurologically worsened patients and unchanged vs changed muscles MEPs at the end of the surgical procedure. In order to stratify the variations of muscle MEPs during surgery, two post hoc thresholds were adopted in order to verify the accuracy of the different kind and number of muscles used for MEP monitoring to predict a neurological worsening: reduction below 50% and 80% of the baseline value[29,30].

Receiver operating characteristic (ROC) curves were built to determine the best cutoff of different muscles used for MEPs monitoring and the areas under the curve (AUC) were calculated to estimate accuracy. Ratios, sensitivity, and specificity of all muscles were determined by using different cutoff amplitude.

Results

Clinical outcome

After surgery, a total of 78 patients (50%) showed absent or mild motor deficits. More specifically, out of 78 patients, 58 patients (74%) remained neurologically intact after surgery whereas 20 patients (26%) showed mild new motor deficits (mean worsening of <1 MRC grade). A total of 54 patients (34%) showed moderate motor deficit after surgery (mean MRC between 2 and 4); out of them, 9 patients (26%) showed stability of the preoperative neurological status, 10 patients (28%) showed mild worsening of the preoperative status (mean worsening of <1 MRC grade), 25 patients (46%) showed moderate worsening of the preoperative status (mean worsening between 1 and 2 MRC grades) and 10 patients (28%) presented a severe worsening of the preoperative status (mean worsening of >2 MRC grades). A total of 25 patients (16%) showed severe motor deficit after surgery (mean MRC < 2); out of them, 3 patients (12%) showed mild worsening of the preoperative status (mean worsening of <1 MRC grade), 2 patients (8%) showed moderated worsening (mean worsening between 1 and 2 MRC grades); the remaining 20 patients (80%) showed severe worsening of the preoperative status (mean worsening of >2 MRC grades). A postoperative CT scan revealed hematoma of the surgical field in 18 cases with need for surgical evacuation in 4 cases; of these 4 patients, 3 showed a mean MRC grade deterioration of -2.5 after surgery and then after the evacuation of the hematoma recovered to -1.3 grades, the last patient did not recover (mean MRC <2 at discharge). A subdural hematoma was revealed in 9 cases with need for evacuation in 1 case with final complete recovery of the preoperative MRC grade at discharge; marked postoperative edema was present at the postoperative CT scan in 31 cases and required prolonged medical therapy in 3 cases.

At discharge the motor status varied as follows: 108 patients (69%) showed absent or mild motor deficits; 69 patients (64%) did not show any deterioration of the preoperative status, 23 patients (21%) showed a mild worsening of the preoperative status (an average deterioration of 0.5 MRC grades) and 16 patients (15%) showed an amelioration of the preoperative status. A moderate motor deficit was present in 42 cases (27%): 3 patients (7%) remained stable, 5 patients (12%) showed an amelioration of symptoms (average MRC grade improvement + 0.9), 15 patients (36%) showed mild deterioration (mean worsening of <1 MRC grade), 13 patients (31%) showed a moderate deterioration (mean worsening between 1 and 2 MRC grades) and 6 patients (14%) showed a severe deterioration (mean worsening of >2 MRC grades). A severe motor deficit was present in 7 patients (4%): 1 patient (14%) remained stable, 1 patient (14%) showed a moderate motor worsening and 5 patients (72%) showed a severe motor deficit, as compared to preoperatively.

The average follow-up range was 3.4 months (range 3 - 9.9 months). The final clinical outcome varied as follows. A total of 123 patients did not show any new motor deficit at follow-up after surgery and more specifically 100 patients (81%) remained neurologically stable (no deterioration from the preoperative status) whereas 23 patients (19%) ameliorated as compared to the preoperative status with an average of

+0.8 MRC grades. Out of these 123 patients, 37 cases (30%) presented after surgery a new motor deficit which completely recovered at the time of follow-up (temporary deficits): in this group, the mean variation of MRC grade after surgery was -1.2 (clinical deterioration after surgery) followed by a mean variation MRC grade of +0.7 (clinical improvement) at discharge and +1.7 at follow-up. A total of 21 patients (14%) showed a mild persistent motor deficit (MRC between 4 and 5) at follow-up with a final average variation of the preoperative MRC grade of -0.6; 9 patients (6%) showed a persistent moderate persistent motor deficit (MRC between 2 and 4) with a final average MRC grade variation of -1.8; 4 patients (2%) showed a persistent severe motor deficit (MRC < 2) with a final average MRC grade deterioration of -3.0.

Intraoperative neurophysiology

Preoperative factors influencing motor outcome. The average number of muscles used for MEPs monitoring was 3. The upper extremities MEPs were recorded from the abductor pollicis (AP) brevis in 144 cases, from the extensor digitorum longus (EC) in 128 cases and from the brachial biceps (BB) in 28 cases; the lower extremities MEPs were recorded from the tibialis anterior (TA) in 71 cases whereas from the abductor hallucis (AA) in 68 cases.

A multivariate analysis of preoperative determining factors on MEPs monitoring reliability showed that the location of the tumor in the prefrontal cortex - posterior segment of II frontal gyrus and SMA - (p=0.04) and along the CST (p=0.008) are related with a higher rate of postoperative permanent deficit (clinical condition established at follow-up). Patients operated for tumor in the prefrontal area (34 cases) showed a clinical deterioration after surgery in 18 cases with 9 of them with MRC grade < 2; a significant deterioration of MEPs were reported in 3 cases (16.6%). An increase of the amplitude at the end of surgery was reported in 14 cases and 5 (27.7%) of them presented a clinical deterioration after surgery. Out of 18 cases, 8 recovered completely by the time of discharge, whereas 10 patients showed an ameliorated but persistent deficit at follow-up.

The pre-existent use of antiepileptic drugs did not influence the reliability of MEPs monitoring on final outcome (p=0.1). The probability of a long-term deficit in case of a tumor located in the prefrontal cortex or along the CST together with a pre-existing deficit and antiepileptic therapy before surgery was 71% (p<0.001). On the opposite, a case of a tumor located in sites different from the prefrontal cortex and along the CST, no preoperative deficits and antiepileptic therapy were related to a risk of postoperative long-term deficit of 8% (p=0.04). The rate of intraoperative seizures was 9% and we found no influence on the final clinical outcome.

Muscle MEP and motor outcome. Different muscles adopted for MEPs monitoring were evaluated in their capability to predict a postoperative motor deficit by a post-hoc analysis on 50% and 80% thresholds. If the MEPs recorded from the abductor pollicis brevis was below the 50% threshold at the end of surgery the probability of a new deficit was 25% (p=0.05) and it raised to 51% if the threshold was set to 80% (p=0.009); if the MEPs recorded from the extensor digitorum longus was over the 50% threshold the probability of a new deficit was 19% (p<0.001) and 20% with a 80% threshold (p<0.001) whereas if the amplitude fell below the 50% threshold the probability raised to 59.8% (p<0.001) and to 80% with a 80% threshold (p<0.001). Recording from the legs, if the MEPs recorded from the tibialis anterior was below the 50% threshold, the probability of new deficit was 30% (p=0.02) and it raised to 69% with an 80% threshold (p<0.001); if the MEPs recorded from the abductor hallucis fell under the 50% threshold, the probability of new deficit was 47% (p<0.001) and it raised to 65% if the threshold was set at 80% (p<0.001).

A logistic regression was used to evaluate the weight of different number of muscles with recorded MEPs below the 50% threshold: if no recorded MEPs was below the threshold at the end of surgery, the probability of a new permanent deficit was 14% (p<0.001); if the MEPs amplitude was below the threshold in one muscle at the end of surgery the probability raised to 37% (p<0.001) and to 63% (p<0.001) if the MEPs amplitude was below the threshold in 2 muscles. No further probability related to incremental number of muscles was tested due to the small sample size of patients with MEPs amplitude reduction in more than 2 muscles. With a threshold set at 80%, the probability of a new stable deficit with no MEPs below the threshold was 15% (p<0.001) whereas it raised to 61% if the MEPs recorded from one muscle was below the threshold at the end of surgery (p<0.001). No further tests were plotted due to the small sample size of patients with multiple MEPs decrease, as previously mentioned. We found no differences in terms of overall capability to predict a new deficit of a single muscle over the others.

In order to evaluate the sensitivity and specificity of different thresholds in the prediction of post-operative neurological worsening, a receiver operating characteristic (ROC) curves were calculated as follows: 1. An overall evaluation was calculated considering only the muscle with the higher variation of amplitude 2. An evaluation of each single muscle was plotted to evaluate the reliability of each muscle from whom MEPs are recorded; the calculated area under the curves defines the reliability of the MEPs recorded from every muscle tested (Fig 1.1, 1.2 and 1.3.). Data regarding the overall sensitivity and specificity for different threshold is reported in table 1.3. and for each muscle in tables 1.4 to 1.8.

Table 1.3. Overall sensitivity and specificity values according to different threshold, calculated with ROC curves (see fig. 1.1).

Thresholds	*Sensitivity*	*Specificity*
10%	79%	44%
20%	76%	56%
30%	70%	63%
40%	64%	79%
50%	***58%***	***82%***
60%	55%	89%
80%	***44%***	***95%***
90%	44%	98%

ROC= receiver operating characteristic

Table 1.4. Sensitivity and specificity values of brachial biceps MEP according to different threshold, calculated with ROC curves (see fig. 1.2a). The reported threshold are fewer than in tab. 1.3 due to small sample size.

Thresholds	*Sensitivity*	*Specificity*
10%	80%	82%
30%	60%	94%
80%	***20%***	***94%***
90%	20%	100%

MEP=motor evoked potential, ROC= receiver operating characteristic

Table 1.5. Sensitivity and specificity values of abductor pollicis brevis MEP according to different threshold, calculated with ROC curves (see fig. 1.2b).

Thresholds	*Sensitivity*	*Specificity*
10%	60%	72%
20%	60%	79%
30%	53%	81%
40%	43%	87%
50%	***43%***	***90%***
60%	40%	92%
80%	***36%***	***94%***
90%	33%	98%

MEP=*motor evoked potential,* ROC= *receiver operating characteristic*

Table 1.6. Sensitivity and specificity values of extensor digitorum longus MEP according to different threshold, calculated with ROC curves (see fig. 1.2c).

Thresholds	*Sensitivity*	*Specificity*
10%	54%	68%
20%	50%	75%
30%	41%	80%
40%	29%	85%
50%	***29%***	***95%***
60%	29%	96%
80%	***29%***	***98%***
90%	16%	100%

MEP=*motor evoked potential,* ROC= *receiver operating characteristic*

Table 1.7. Sensitivity and specificity values of tibialis anterior MEP according to different threshold, calculated with ROC curves (see fig. 1.3a).

Thresholds	*Sensitivity*	*Specificity*
10%	52%	63%
20%	47%	71%
30%	41%	78%
40%	41%	80%
50%	***35%***	***82%***
60%	35%	84%
80%	***29%***	***93%***
90%	17%	97%

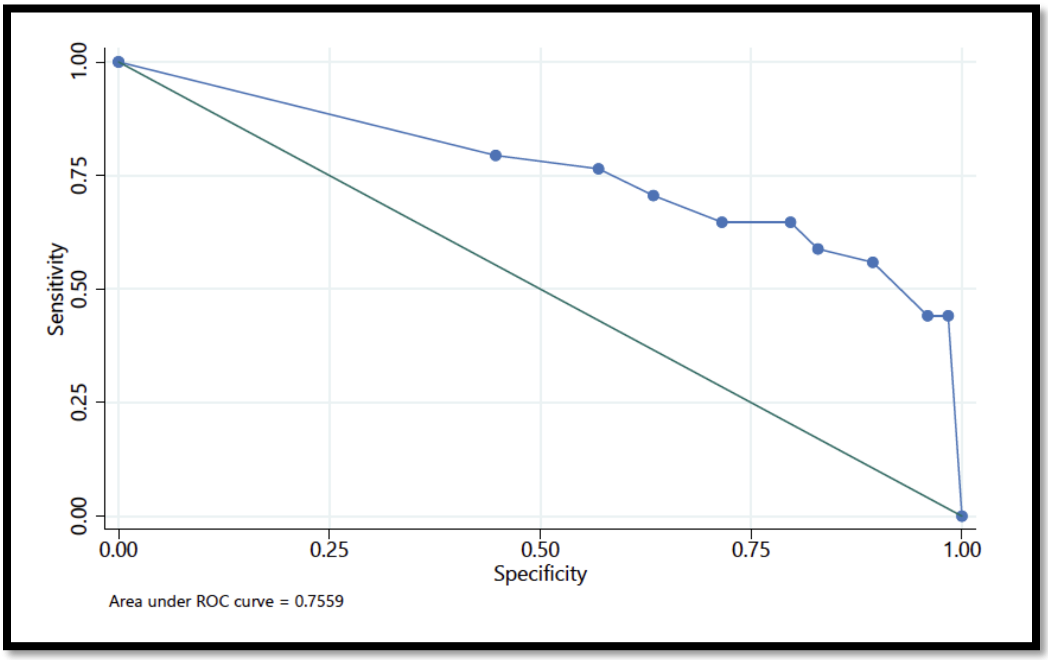
MEP=motor evoked potential, ROC= receiver operating characteristic

Table 1.8. Sensitivity and specificity values of abductor hallucis MEP according to different threshold, calculated with ROC curves (see fig. 1.2a).

Thresholds	*Sensitivity*	*Specificity*
10%	43%	63%
20%	43%	73%
30%	43%	81%
40%	37%	86%
50%	***37%***	***89%***
60%	37%	92%
80%	***37%***	***94%***
90%	25%	94%

MEP=motor evoked potential, ROC= receiver operating characteristic

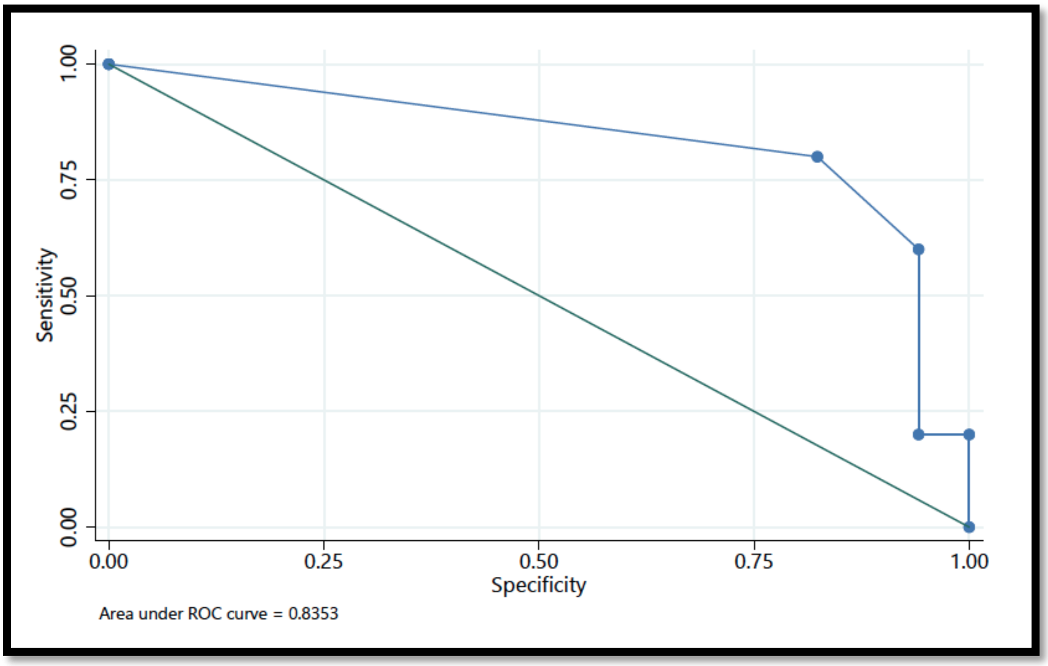
Figure 1.1. Different threshold of sensitivity and specificity defined with ROC curves (table 1.3).



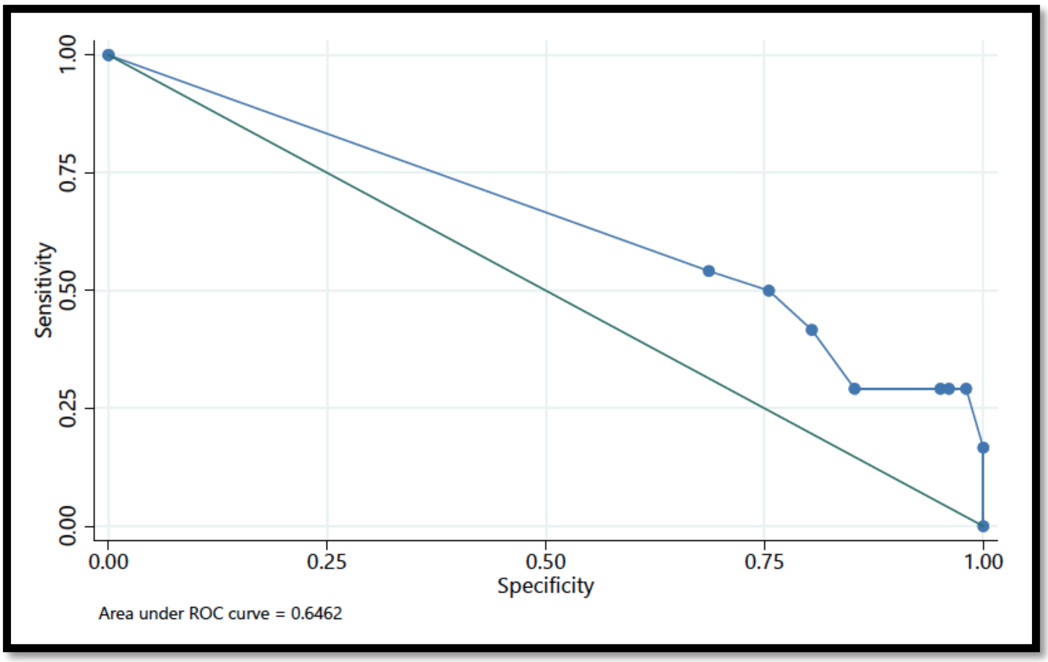
ROC= receiver *operating characteristic*

Figure 2.2. Sensitivity and specificity of arm's muscles used during IONM assisted surgery defined with ROC curves: a. brachial biceps, b. abductor pollicis brevis and c. extensor digitorum longus.

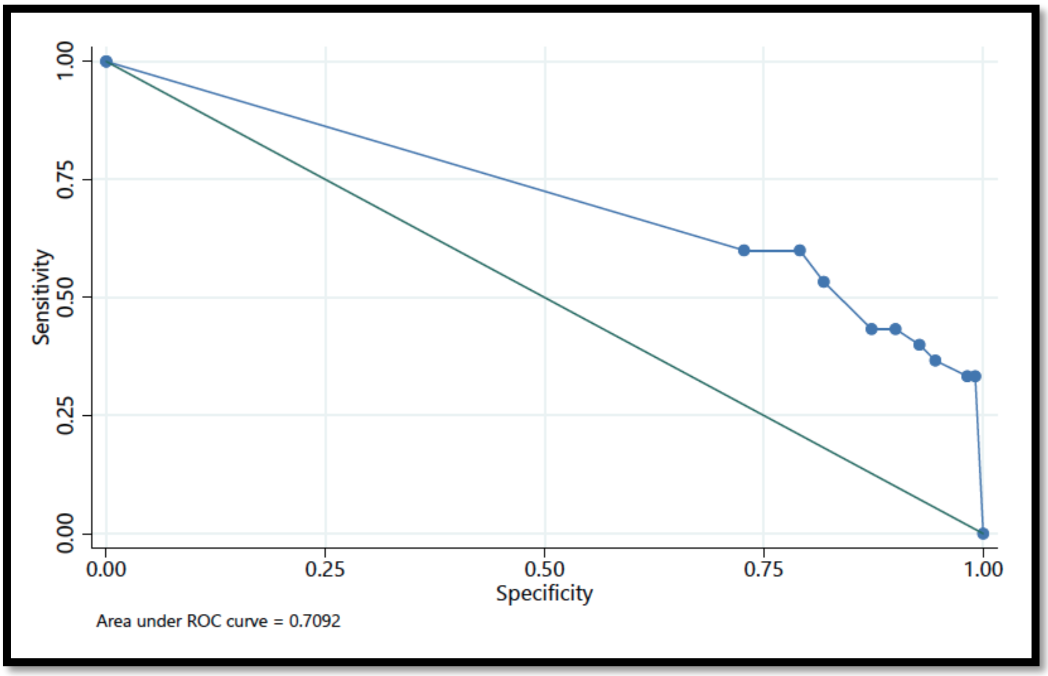
a



b



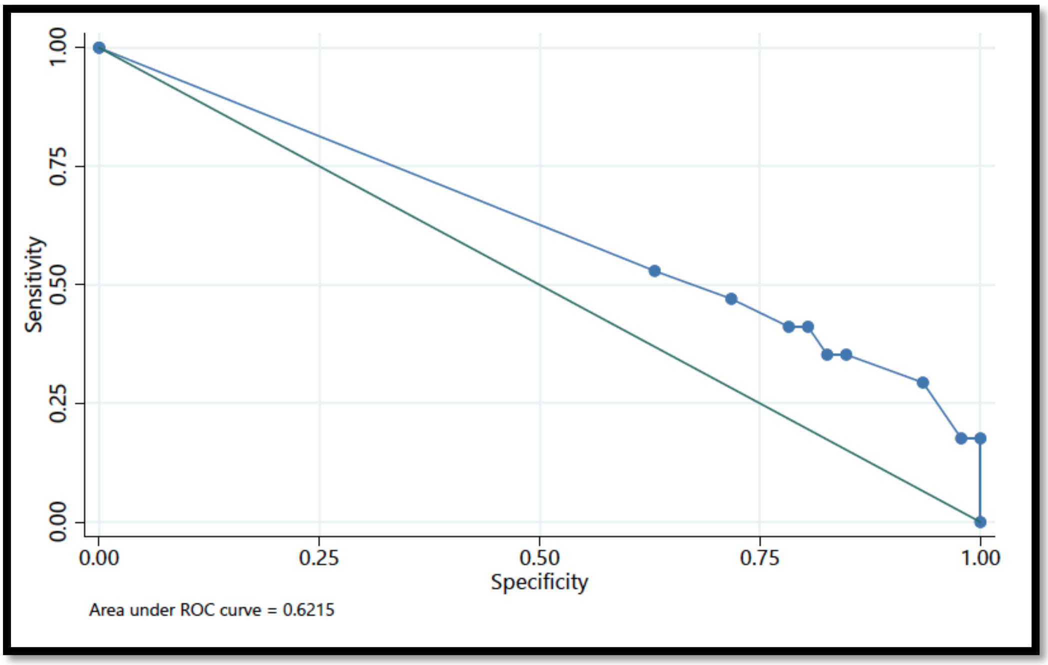
c



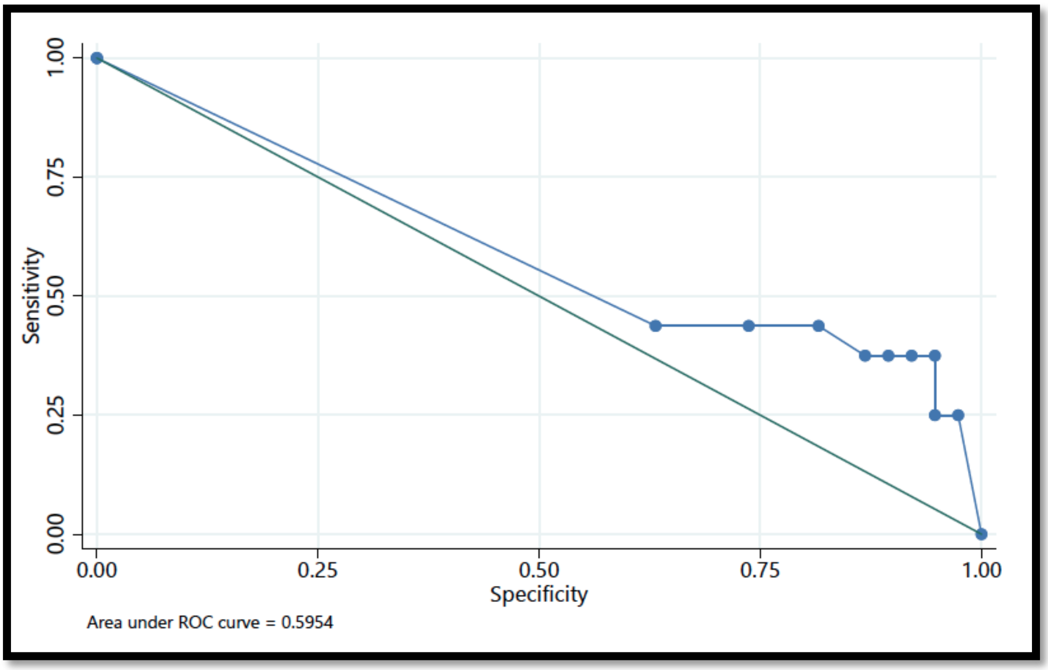
IONM= intraoperative neurophysiological monitoring; ROC= receiver operating characteristic

Figure 1.3. Sensitivity and specificity of leg's muscles used during IONM assisted surgery defined with ROC curves: a. tibialis anterior, b. abductor hallucis.

a



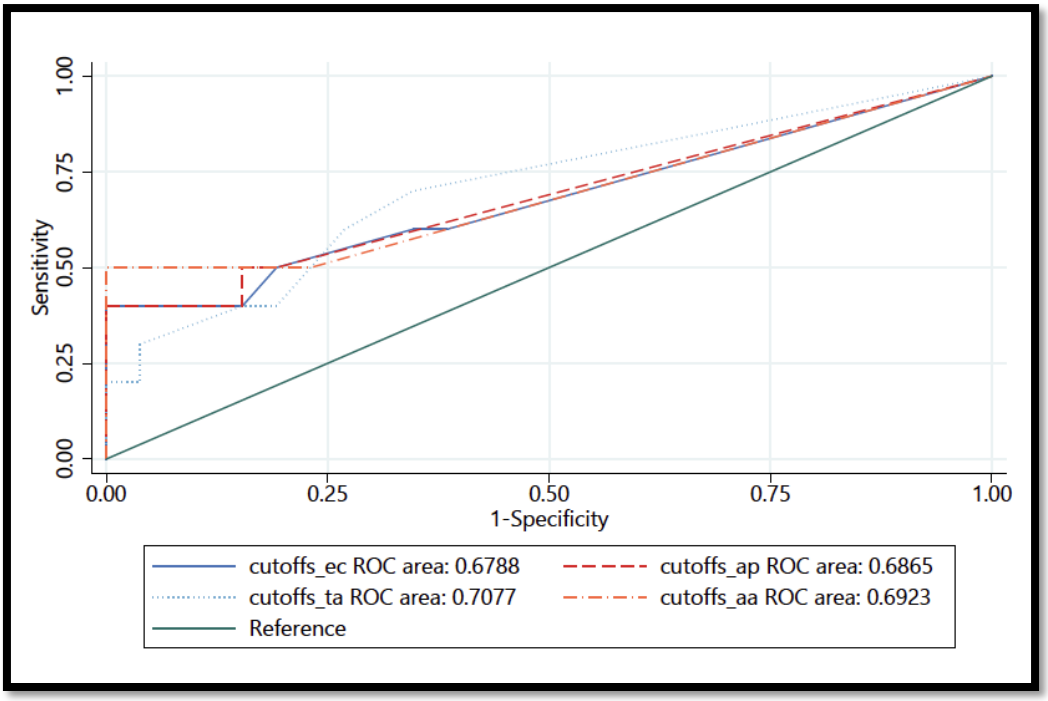
b



IONM= intraoperative neurophysiological monitoring; ROC= receiver operating characteristic

In 36 cases (23%), it was possible to have contemporary MEPs recordings from 4 different muscles (AP, EC, TA and AA) during all the surgical procedure. A ROC curve was plotted in order to obtain in such a circumstance the relationship between the muscle with higher variation of amplitude during surgery and the rate of postoperative stable motor deficit. The ROC curve of the TA (fig. 1.9) resulted with the higher area under the curve (0.707).

Figure 1.9. Sensitivity and specificity of four different muscles in a condition of continuously MEPs monitoring from all four muscles (abductor pollicis brevis - AP, extensor digitorum longus - EC, tibialis anterior - TA and abductor hallucis - AA) defined with ROC curves.



MEPs= motor evoked potentials; ROC= receiver operating characteristic

ROC curves were used to define the sensitivity and specificity of different MEPs amplitude threshold for the prediction of postoperative neurological worsening according to different tumor locations. We limited this analysis for tumors located in the prefrontal cortex, insula and pre-post central gyrus due to the relatively small sample size of the other tumor locations. Data regarding sensitivity and specificity of MEPs monitoring according to the aforementioned regions are reported in table 1.9

to 1.12 and in figure 1.10 to 1.13. Sensitivity and specificity for different threshold are calculated for each tumor location according to the sample size.

Table 1.9. Sensitivity and specificity values for different threshold related to tumors located in the prefrontal cortex, calculated with ROC curves (see fig. 1.10).

Thresholds	*Sensitivity*	*Specificity*
10%	50%	40%
20%	50%	50%
30%	40%	63%
40%	30%	77%
50%	***30%***	***90%***
80%	***30%***	***95%***
90%	20%	100%

ROC= receiver *operating characteristic*

Table 1.10. Sensitivity and specificity values for different threshold related to tumors located in the insula, calculated with ROC curves (see fig. 1.11).

Thresholds	*Sensitivity*	*Specificity*
10%	100%	52%
20%	100%	60%
40%	100%	65%
50%	***100%***	***73%***
60%	87%	78%
80%	***87%***	***91%***
90%	75%	95%

ROC= receiver operating characteristic

Table 1.11. Sensitivity and specificity values for different threshold related to tumors located in M1, calculated with ROC curves (see fig. 1.12).

Thresholds	*Sensitivity*	*Specificity*
10%	100%	57%
20%	75%	66%
30%	75%	76%
40%	75%	85%
80%	***75%***	***90%***
90%	50%	100%

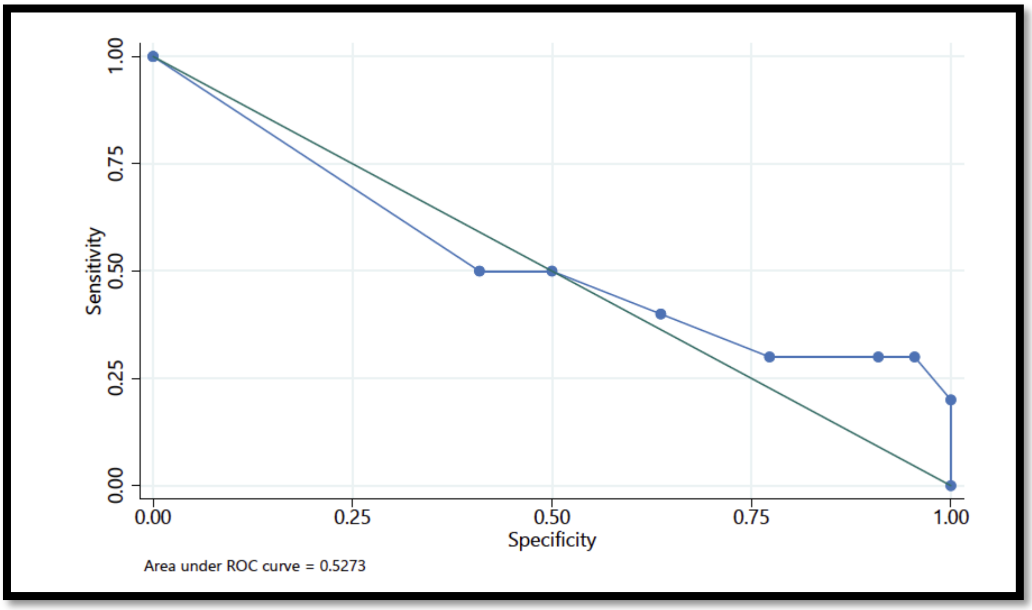
ROC= receiver operating characteristic

Table 1.12. Sensitivity and specificity values for different threshold related to tumors located in the S1 gyrus, calculated with ROC curves (see fig. 1.13).

Thresholds	*Sensitivity*	*Specificity*
10%	100%	45%
30%	100%	65%
40%	100%	80%
50%	***100%***	***85%***
60%	100%	90%
80%	***50%***	***90%***
90%	50%	100%

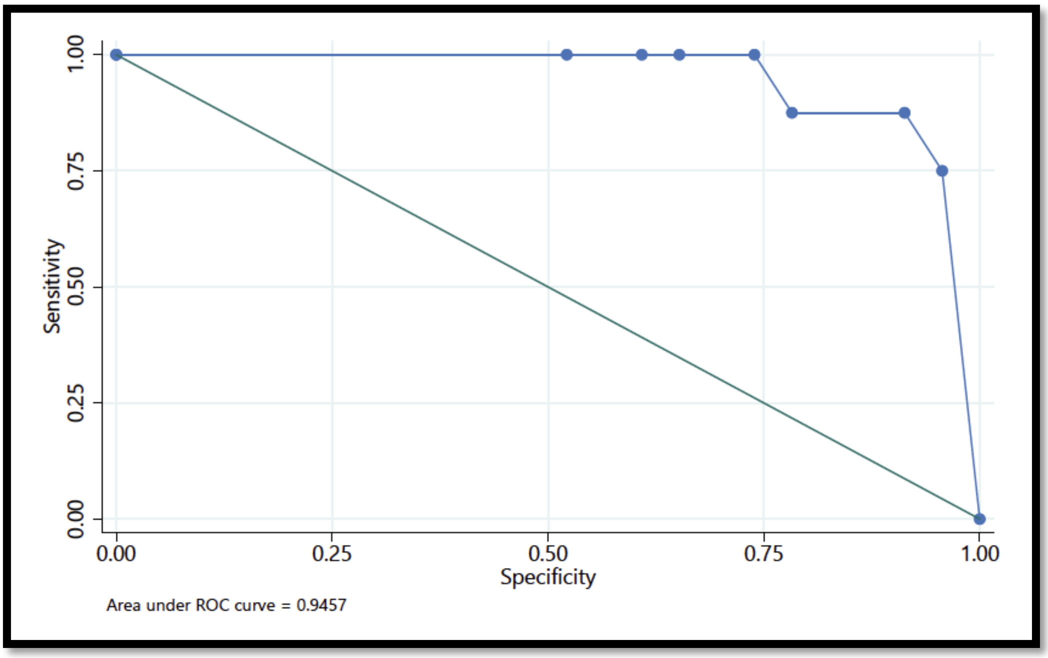
ROC= receiver operating characteristic

Figure 1.10. Sensitivity and specificity of MEP monitoring for tumors located in the prefrontal cortex defined with ROC curves.



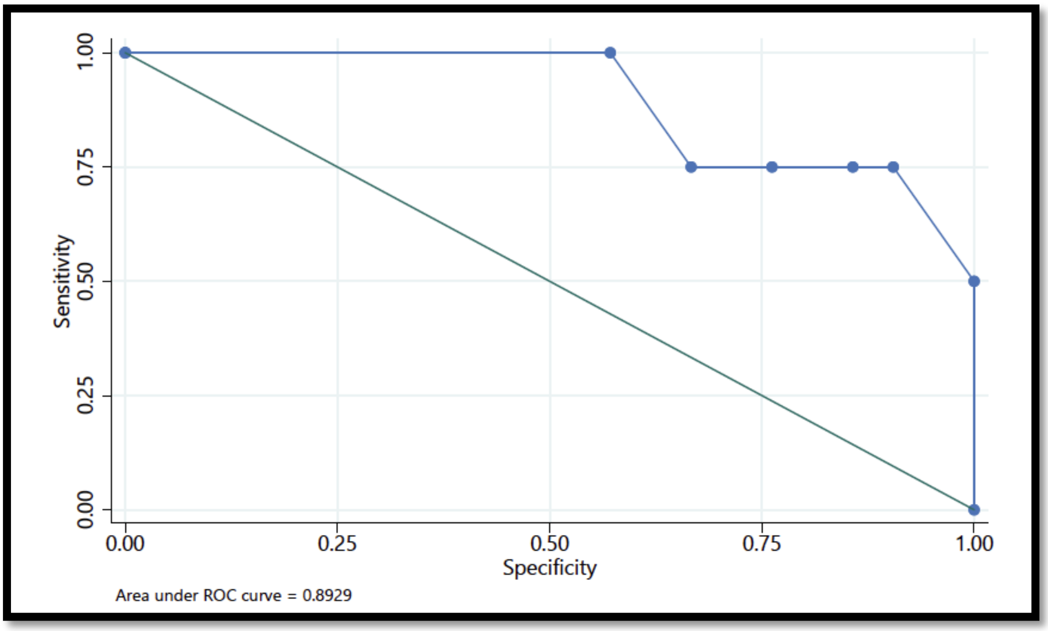
MEP= motor evoked potential; ROC= *receiver* operating characteristic

Figure 1.11. Sensitivity and specificity of MEP monitoring for tumors located in the insula defined with ROC curves.



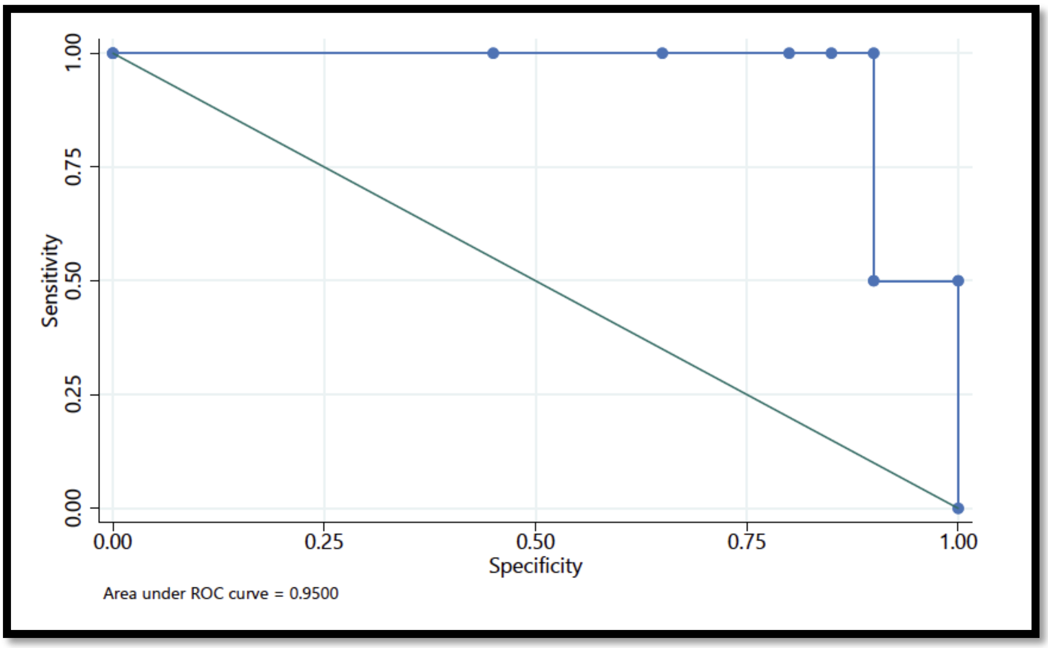
MEP= motor evoked potential; ROC= *receiver* operating characteristic

Figure 1.12. Sensitivity and specificity of MEP monitoring for tumors located in M1 defined with ROC *curves.*



MEP= motor evoked potential; ROC= *receiver* operating characteristic

Figure 1.13. Sensitivity and specificity of MEP monitoring for tumors located in the S1 defined with ROC *curves.*



MEP= motor evoked potential; ROC= *receiver* operating characteristic

Discussion

Muscle MEPs monitoring are confirmed as undeniable IOM tool during surgery for brain tumors in motor areas. Our data confirmed the overall reliability of the method, final predictive value of IOM can be influenced by various preoperative and intraoperative variables. The preoperative condition of the patients, the location of the tumor in the prefrontal cortex and/or along the corticospinal tracts reduce the reliability of MEPs monitoring. On the other hand, the differences in the modality of MEPs application between different patients (different muscles, different number of muscle contemporary available for MEPs monitoring) may introduce a bias during the "on line" interpretation of MEPs changes during surgery. Our study highlighted the different probability of final long-term paresis related to the different muscle from whom the MEPs deterioration is recorded and the final value of MEPs changes among different muscles.

It should be note that the present study was designed as retrospective and based on post hoc analysis of muscle MEPs changes at the end of surgery, making a comparison between pre- and postoperative neurological status of the patients in a 2 x 2 fashion. From a methodological standpoint, this construction caused an incomplete evaluation on how reversible changes of muscle MEPs can cause intraoperative surgical maneuvers that could eventually had affected the clinical outcome of patients. As highlighted by Skinner[55], reversible EP changes represent a particular problem because a surgical intervention in response to muscle MEP decline occurs before execution of the reference standard, that is intraoperative or postoperative wake up. Hill described nine guidelines of evidence for causation when an association is observed between two variables[21] and these guidelines has been adopted by Skinner to deploy a Bayesian adjustment of posttest probability[55] in order to introduce a balance between reversible changes considered irrelevant (or true negative) and reversible changes considered always as true positive. The value of this approach is clearly exampled in vascular neurosurgery: during the exclusion of an aneurysm, the inadvertent occlusion of a perforator hidden by the aneurysm produces a decrease in muscle MEPs amplitude which is reported to the surgeon; the clip is removed and the muscle MEPs restored. At the end of surgery, if compared to the baseline values, there is no change of the EPs, however the reversible changes during surgery prevented an almost sure new post-operative deficit. In our scenario, we were not able to provide a post hoc evaluation of the reversible changes and their impact on clinical outcome due to the retrospective design of the study. However, we believed that the large number of patients evaluated provide a sufficient data to verify our hypotheses.

Muscle MEPs monitoring is a well-established IONM technique, based on transcranial (TES) and direct (DCS) electrical stimulation. The application of DCS was described by Taniguchi et al in 1993[58], earlier than the application of TES. The application of DCS MEP monitoring gained attention in the subsequent years, with larger application of the technique during surgery in motor areas[26,49]. Seidel et al[54] described their experience during surgery for peri-central brain tumors in 100 consecutive patients. The authors stated that unchanged or reversible DCS MEP findings gave a 100% negative predictive value for postoperative deficit at 3 months. On the other hand, given the fact that “irreversible change” is a post hoc definition, irreversible DCS MEP change is a suboptimal indicator during surgery. According to Seidel et al[54], direct surgical damage occurred at a statistically significant lower rate when the subcortical stimulation intensity is > 4 mA and since the incidence of decreased neurologic deficit at 3 months was relatively low for thresholds of 1 to 3 mA, the safe subcortical stimulation threshold for resection could be pushed as low as 2 mA. It should be kept in mind that in brain surgery with critical vicinity to the motor cortex or to the corticospinal tract, new motor impairment despite preserved intraoperative MEP might occur through a number of different mechanisms. An excessive intensity of stimulation for TES MEP monitoring may lead to elicitation of CST action potentials caudal to the target territory, and true damage to the CST may remain unnoticed. Thus, keeping the stimulation current intensity at a slightly supra-threshold level for stable MEP responses it is of paramount importance[57]. In our series, subcortical location of the tumour along the CST was related to a significant risk for postoperative deficits and patients submitted to subcortical mapping (53% of patients with a tumour along the CST) showed a slightly worse clinical outcome than patients “not mapped”; however, one should keep in mind that subcortical mapping is applied for patients at a very high risk of new postoperative motor deficit due to the location of the tumour and furthermore it should be noted that for this specific location patients submitted to subcortical mapping harboured a glioblastoma in 70% of cases and the mean MRC grade at admission was slightly worse than patients not submitted to subcortical mapping (4.3 for mapped vs 4.6 for not mapped). We believe that the reason for the apparent failure of subcortical mapping was mainly due to the intrinsic characteristics of the tumour together with a surgical pursue of radical resection[42]. The analysis of our data pointed out that also the prefrontal cortex bears a significant risk for long term deficit (p=0.04) but with a high rate of false negative results of MEP: after surgery, 9 patients out of 34 cases presented a severe motor deterioration (MRC grade <2) and a total of 10 cases out of 34 (29%) showed persistent motor deficit at follow-up. MEP changes were recorded only in 3 cases out of 34 patients monitored. A possible explanation for this high rate of false negative results is related to the inability of IONM to evaluate different cortical motor networks apart from M1 and CST. Penfield and Welsh[44] reported that, although the most frequent effect of direct electrical stimulation of the SMA was inhibition of voluntary motor and speech activity, the unilateral excision of the SMA did not produce a permanent motor deficit. However, in the first few days after surgery, when the SMA syndrome is complete, hypokinesia can be so severe as to resemble the clinical picture of hemiplegia. Experimental studies on connections between M1 and the nearby cortex in monkeys, highlighted a marked difference in connection organization between the anterior motor areas and the posterior motor areas: The posterior motor areas receive their main cortical input form the parietal lobe ("parieto-dependent" motor areas). In contrast, the anterior motor areas receive their main cortical connections from the prefrontal cortex ("prefronto-dependent" motor areas)[33]. The prefronto-dependent areas do not send projections to M1, but have diffuse connections with the other motor areas[32]; furthermore, they do not project directly to the spinal cord[20]. In this view the parieto-dependent areas receive rich sensory information originating from the parietal lobe and use it for action; on the other hand, prefrontal-dependent areas receive higher order cognitive information, related to long-term motor plans and motivation[47]. In this setting, the deterioration of patients treated for tumours in the prefrontal cortex is related to a damage to the prefrontal network which cannot be investigated by MEP monitoring. However, making a comparison between the two previously reported regions, one should keep in mind that the direct damage of M1 or CST is related with more severe and persistent motor deficits than premotor, prefrontal or SMA damage and this is the reason why the goal of surgery is to preserve them. The ability of DCS MEPs monitoring is to guide surgery around M1 and along

CST but a damage produced in other regions connected in network with these regions do not necessarily produce a DCS MEPs changes. On the other hand, it should be emphasised that especially with large bundles of fibers, it is impossible to provide a perfect information on their functional status[34].

Different application of amplitude threshold has been adopted in order to overcome false negative results related to "intermediate" changes of MEP. The 50% and 80% threshold have been described by many authors[25,29,30,37]. Our data showed that the capability of muscle MEP deterioration to predict a neurological deficit had an overall sensitivity of 58% and specificity of 82% for a threshold set at 50% of the baseline values and a sensitivity of 44% and specificity of 95% for a threshold set at 80%. Evaluating the sensitivity and specificity of each muscle with the same purpose as reported above, we found the higher values from abductor pollicis brevis recordings: 43% sensitivity and 90% specificity for the 50% threshold and 36% sensitivity and 94% specificity for the 80% threshold. On the other hand, the ROC curves of sensitivity and specificity in case of 4 muscles monitored together during all the procedure (36 cases) revealed a higher ROC area for the tibialis muscle. Due to wider cortical area related to the movement of the hand and the usual exposure of this region during surgery in motor areas, one should expect the easier and stronger stability for MEP monitoring obtained through stimulation of the hand/superior limb areas. Our data findings confirmed this relationship, showing higher sensitivity and specificity for superior limb muscle. However, plotting together the simultaneous MEP monitoring from 4 different muscles for all the procedure, the higher reliability was found from inferior limb muscle. Keeping in mind that these latter data are obtained from only 36 cases (23%), one can argue that the clinical evaluation of the strength deficit arising from tibialis anterior dysfunction can be easier to evaluate and graduate according to the MRC scale in comparison with the movement of the hand; furthermore, motor units related with the activation of the tibialis anterior muscle are less than the motor units for the activation of hand muscle thus if the MEP from tibialis anterior is changed during surgery, the probability for direct damage is reasonable higher.

According to the threshold applied in the post-hoc analysis, we found different probabilities for final motor deficit according to the different muscles from whom the MEP was recorded; the higher probabilities of motor deficit were related to a decrease below the threshold of the MEP from arms. Furthermore, as predictable, more than 1 muscle with MEP below the threshold is related with a higher probability of final motor deterioration.

Weaknesses of the present study are the retrospective design as previously stated and the fact that the overall number of patients with intraoperative significant MEP changes are quite low (MEP loss happened in only 6 cases) thus this could influence the final analysis of IONM data and its relationship with the clinical outcome.

The difficulties that are found in the attempt to organize and classify all the intraoperative deterioration of MEP highlight the intrinsic limits of the method: DCS MEP monitoring is a valuable technique to prevent or at least to limit the onset of new motor deficit, however it can be influenced in its efficacy by multiple factors. The real limit of the technique is the inability to provide a reliable prediction on the clinical outcome following the aforementioned intraoperative scenarios of intermediate MEP changes. Furthermore, the amplitude variability expressed by muscle MEPs makes baseline selection and amplitude reduction criteria problematic and this is due to their polysynaptic origin. In this view, a stronger predictor for long term outcome is desirable, especially when a tailored approach is needed. Patients with glioblastoma in the peri-motor cortex, given their short life expectancy, should undergo a resection that must be as safe as possible in order to guarantee the QOL of patients after surgery. On the other hand, a radical resection should be pursued in patients with LGGs to warrant a prolonged survival. Therefore, for patients with LGGs, even if the risk of transient postoperative deficit is higher when attempting a radical resection, this may be acceptable as long as the motor deficit is reversible. However, such tailored approach is not completely feasible due to the incomplete relationship of intraoperative neurophysiological data and postoperative clinical data.

Conclusions

According to our data, the prefrontal cortex and along the CST are related with a higher rate of postoperative motor deficits ($p=0.04$ and $p=0.008$, respectively); for tumours located in the prefrontal cortex, 53% of patients showed new motor deficit with deterioration of MEP in 16.6% of them and increase of MEP amplitude in 27.7% of cases. Different muscles showed different capability to predict new motor deficits; according to our data, the higher is the number of muscles with MEP amplitude below the threshold, the higher is the probability of a new stable motor deficit.

SECTION 2: INTRAOPERATIVE NEUROPHYSIOLOGY DURING SURGERY FOR INTRAMEDULLARY SPINAL CORD TUMORS: THE ROLE OF D-WAVE MONITORING.

Background

The surgical removal of an intramedullary spinal cord tumor (ISCTs) bears a high risk of new postoperative motor deficits. Furthermore, the tiny diameter of the spinal cord and the high number of packed descending and ascending bundles of fibers reduce the tolerance of surgical manipulation and dissection maneuvers.

Surgery for ISCTs had required an extraordinary development of technology in order to obtain a standard IOM setting which was able to predict and possible to prevent the risk of postoperative motor deficit[6,28]. The introduction of somatosensory evoked potentials (SSEPs) in 1980 represented the first step into the field of IOM for ISCTs. However, the fact that SSEPs could not detect injury to the motor pathways, created a high number of “falsely-negative” labeled results (namely, no SSEPs deterioration during surgery and new postoperative motor deficit after surgery). This was, though, a misleading terminology because we should not expect SSEPs to detect motor injury. The application of transcranial electrical stimulation (TES) to elicit motor evoked potentials (MEP) started in 1990s and then acquired a higher and higher relevance in the management of ISCTs. Moreover, the use of D-wave monitoring during surgery with precise alarm criteria and uniform management of critical situation has helped to standardize the surgical management of ISCTs[28]. Furthermore, the strong reliability of D-wave monitoring as predictor for long-term motor deficit underlined that its application must be standardized during surgery for ISCTs. Yet, very few studies specifically addressed D-wave monitoring and data on its reliability in large clinical series are still lacking[10,13,28,50].

Therefore, taking advantage from the fact that approximately 300 ISCTs have been operated with IONM at our institution over the past 17 years, we reviewed our experience to confirm the hypothesis that maintaining the amplitude of the D-wave above 50% of the baseline value is the best predictor of good long-term motor outcome.

Methods

Patients population

A retrospective chart review was conducted on 219 patients (117 males) with mean age 41.8 years (range 8 - 84 years), who were submitted to IONM assisted surgery for ISCTs at the Neurosurgical Institute of Verona between January 2000 to December 2017; all patients of the study had at least 6 months of follow-up; there were 24 pediatrics patients (< 18 years-old).

Neurological and radiological assessment

The main clinical presentation was pain (105), sensory disturbances (63), motor symptoms (39) and vertigo (5). In 7 cases the diagnosis was incidental: during scheduled radiological exams for trauma (2), in the follow-up after brain tumor resection (2) and ISCT (1), during the follow-up for neurofibromatosis 1 and Von Hippel-Lindau disease (2). In 34 patients (15.5% of cases) urinary sphincter impairment was present at the diagnosis. Patients with presenting with motor deficit showed a trend towards a shorter duration of symptoms (average 18.2 months) as compared to those who presented with sensory symptoms (average 24.0 months) and pain (average 26.7 months).

According to the McCormick scale (table 2.1), 103 patients were in grade I (47%), 85 patients in grade II (38.8%), 24 patients in grade III (11%) and 7 in grade IV (3.2%). Globally, 188 patients (86%) were able to walk independently at the time of the admission (McCormick grade I and II).

Table 2.1: McCormick scale for functional classification of intramedullary spinal cord tumors (ISCTs).

Grade	Characteristics
I	Neurologically normal, mild focal deficits, normal gait
II	Sensorimotor deficits affecting function, severe pain, gait difficulties, can still walk
III	Moderate motor deficit, needs cane for ambulation, ± arms affected, ± independent
IV	As above ± arms affected, usually not independent

The tumor locations were the cervical (114), the cervico-thoracic (32) and the thoraco-lumbar spinal cord (73). The average extension of the tumor was 2.9 levels (range 1 - 9 levels). In 82 cases the tumor was cystic. Syringomyelia close to the tumor was present in 57 cases: the location of the syrinx was cranial (7), caudal (12) and both cranial and caudal to the tumor (38).

All the patients were operated on in prone position except for 18 patients with a bulbo-cervical tumor (8,2%) who were operated on with the semi-sitting position. The extent of resection was considered radical in 174 cases (79%), near-radical 17 cases (7.8%) and partial in 18 cases (8%); 10 patients were submitted to biopsy of the tumor (5%).

The lesions were ependymomas (120), astrocytomas (52), cavernomas (20), hemangioblastomas (14) and melanocytic tumors (3). Overall, in 10 patients (4.6%) the tumor was metastatic (7 cases of hemangioblastomas and 3 cases of melanocytic tumors). All the patients with ependymoma were in WHO grade II except one patient who was WHO grade III; in one case, it was not possible to define the grade between grade I and II. The astrocytomas were WHO grade I (29), grade II (3), grade III (14) and grade IV (6).

Intraoperative monitoring settings and alarm criteria

Somatosensory evoked potentials (SSEPs)

Cortical and subcortical SEPs were obtained through stimulation of the median nerve at the wrist and the posterior tibial nerve at the ankle (intensity, 40 mA; duration, 0.2 ms; repetition rate, 4.3 Hz). Recordings were performed via corkscrew needle electrodes inserted in the scalp (CS electrode; Nicolet Biomedical, Madison WI) at CZ=-FZ (legs) and C3=/C4=-FZ (arms), according to the international 10–20 system of electrode placement.

Motor evoked potentials (MEP)

In order to obtain MEP recordings from limb muscles, short trains of five to seven square-wave stimuli of 0.5 ms duration and interstimulus interval of 4 ms were delivered at a repetition rate up to 2 Hz through CS electrodes placed at C1 and C2 scalp sites, according to the 10–20 system of electrode placement. A C1–C2 montage preferentially elicited right extremity MEP, whereas a C2–C1 montage favoured left extremity MEP. In order to reduce muscle twitching, sometimes a Cz-Fz montage was preferred, during MEP monitoring from leg muscles. The stimulation intensity did not exceed 240 mA. MEP recordings were obtained via needle electrodes 3 cm apart inserted into upper and lower extremity muscles. We usually monitored muscle MEP from the abductor pollicis brevis and the extensor digitorum longus for the arm and the tibialis anterior and the abductor hallucis for the leg.

Transcranial Electrical Stimulation and Epidural (D-Wave) Recordings

As soon as the dural surface is exposed, an extradural electrode is placed caudally to the tumour. A single transcranial electrical stimulus was applied, using the same montages for muscle MEP, to elicit a D-wave that was recorded by the aforementioned electrode. Signals were amplified 10,000 times and the bandwidth was amplified 1.5 to 1700 Hz. Baseline D-waves were recorded after exposing the spinal cord.

The instrumentation adopted for stimulation and recordings were the same as in Section 1 (see Section 1 - *Methods*).

Alarm criteria

According to our previous experiences and the literature, the following IONM criteria were applied in order to define and eventually modify the surgical strategy. 1. *SSEPs*: a 50% decrease in amplitude and/or a 10% prolongation in latency were considered significant. During the myelotomy, the surgeon was notified and the procedure temporarily stopped or was moved to a different location along the tumour but if MEP were stable, surgery was continued in all cases. 2. *Muscle MEP*: “presence/absence” criteria were adopted due to the marked trial-to-trial deterioration of muscle MEP amplitudes and because of reports that only mMEP loss consistently correlates to postoperative motor deficits. Muscle MEP were considered absent when no response was recordable using a scale as low as 30 V per division with maximum stimulus intensity. As a minor warning sign, however, the surgeon was notified anytime the MEP amplitude consistently decreased and/or the stimulation intensity to elicit a response progressively increased. 3. *D-wave*: a decrease of more than 50% of the baseline amplitude was considered significant. Decrements of the D-wave amplitude between 30 to 50% of the baseline were considered minor warning signs and were reported to the surgeon but were not critical to the point of stopping surgery. Prolongation of latency was considered not significant because possibly related to deterioration of nonspecific factors such as temperature.

Clinical and surgical management of alarm criteria

Minor modifications of D-wave and/or muscle MEP suggested to move the surgical dissection to a different area, irrigating the surgical field with warm saline, and/or correcting systolic hypotension. On the basis of minor changes, the surgical procedure was never abandoned. The disappearance of MEP with preservation of the D-wave amplitude at more than 50% of the initial value was considered a major change likely to reflect a transient postoperative motor deficit in the affected limb. In this condition, surgery was stopped for a few minutes to allow recovery of the neurophysiological signals, and additional measures, such us irrigation with saline solution, local instillation of papaverine, or induced hypertension, were used selectively. According to the expected relationship between this kind of EPs modification and clinical outcome (long-term outcome not affected), surgery was stopped only in selected cases, mostly due to tumour histological findings, the patient's preoperative motor status, and the failure of evoked potentials recovery after all corrective measures had been taken. Surgery was invariably and immediately stopped when mMEPs were lost and the D-wave decreased by more than 50%; if no recovery of the neurophysiological signals occurred after all corrective measures had been taken, surgery was abandoned. In case of "unmonitorable" D-wave from the beginning of the procedure, the disappearance of MEPs, not reversed by corrective measures, was the criterion to abandon surgery, because this pattern cannot differentiate and predict between transient and permanent motor deficit.

Anesthesia protocol

Total intravenous anesthesia protocol adopted was the same as in section 1 (see Section 1, Methods).

Postoperative evaluation and follow-up

All the patients were evaluated according to the McCormick grade immediately after surgery, at discharge and at follow-up. Deterioration of the MEP and D-wave amplitude were evaluated and related to the clinical outcome at discharge and at follow-up. MEP deterioration was classified in mild (<50% deterioration), moderate (>50% and <80% deterioration) and severe (>80% deterioration) and different deterioration of amplitude were compared to the clinical outcome of patients at discharge and at follow-up.

Statistical analysis

Parametric and nonparametric tests (T-Test and Wilcoxon test) were adopted to compare continuous variables. The Chi-square test and the Fischer exact test were adopted for discrete variables. Univariate and multivariate analyses were applied to multiple factors in order to define their weight on D-wave monitorability. The crude odds ratio (95% confidence interval and relative P value) was calculated using a univariate logistic regression model and then a multivariate logistic regression model simultaneously to estimate the effect of the same factors on D-wave monitorability.

Results

Clinical outcome

After surgery, the average deterioration of the preoperative McCormick grade was of 0.9 grades. A total of 137 patients (62.5%) showed a worsening of about 1 McCormick grade, 81 patients (37%) remained neurologically stable after surgery and 1 patient (0.5%) improved after surgery (table 2.2).

Table 2.2: Differences between preoperative and postoperative McCormick grade after surgery for intramedullary spinal cord tumors (ISCTs).

		Postoperative McCormick Grade				
		-1	0	+1	+2	+3
Preoperative McCormick Grade	I	0	33	32	30	8
	II	1	28	39	17	-
	III	0	13	11	-	-
	IV	0	7	-	-	-
Total		1	81	137		

At discharge, the mean deterioration of the McCormick grade was reduced to 0.6 grades; overall, 100 patients (45.7%) showed a persistent deterioration of the McCormick grade as compared to the preoperative grade, 110 (50.2%) showed a stable

McCormick grade and 9 patients (4.1 %) showed an improvement of the preoperative grade (table 2.3).

Table 2.3: Differences between preoperative and discharge McCormick grade for intramedullary spinal cord tumors (ISCTs).

		McCormick Grade ***at discharge***				
		-1	0	+1	+2	+3
Preoperative McCormick Grade	I	0	50	19	30	4
	II	5	40	34	6	-
	III	3	14	7	-	-
	IV	1	6	-	-	-
Total		9	110	100		

The mean follow-up was 33 months (range 1-202 months). At follow-up, the mean McCormick grade appeared improved (0.5 grades) if compared to the discharge value. Moreover, if compared to the preoperative mean value, the worsening of the motor performance is 0.08 grades. More specifically, a total of 46 patients showed a persistent deterioration of the McCormick grade: 3 patients showed a deterioration of 2 grades whereas 43 patients a deterioration of 1 grade; 123 patients remained stable and 31 patients presented an amelioration of the preoperative McCormick grade (table 2.4).

Table 2.4: Differences between preoperative and follow-up McCormick grade (mean follow-up= 33 months) for intramedullary spinal cord tumors (ISCTs).

		McCormick Grade ***at follow-up***				
		-2	-1	0	+1	+2
Preoperative McCormick Grade	I	0	0	79	26	2
	II	0	26	41	19	1
	III	2	9	9	1	-
	IV	0	0	4	-	-
Total		37		133	49	

Intraoperative neurophysiology

MEP monitoring

MEP were obtained in all cases however in 3 cases the EPs obtained where not considered stable enough for continuous monitoring. MEPs loss was experienced in 8 patients (3.7%). According to the previously defined categories, 56 patients did not show deterioration of MEP during surgery, 57 patients showed a minor deterioration (<50% of the baseline amplitude), 66 patients a moderate deterioration (>50% and <80%) and 29 patients a severe deterioration (>80%) (table 2.5).

Table 2.5: Muscle motor evoked potentials (MEPs) changes during surgeries for 216 intramedullary spinal cord tumors (ISCTs).

MEP amplitude changes	Number of cases
Stable (no changes from baseline)	56
<50% of baseline value	57
Between 50 and 80% of baseline value	66
>80% of baseline value	29
Complete Loss	8
Total	216

Patients with a severe or moderate MEP deterioration during surgery showed a worse motor outcome at discharge (McCormick III and IV) as compared with patients who showed a stable MEP during surgery. More specifically, 69% of patients with a severe decrease of MEP amplitude during surgery showed a motor deterioration after surgery (McCormick III or IV), whereas patients with a moderate reduction of MEP during surgery deteriorated in 51% of cases. At follow-up, patients with an intraoperative moderate/severe deterioration of MEP showed worse outcome than patients with stable intraoperative MEP (p=0.01); overall, 38% of patients with a severe deterioration of MEP showed persistent motor deficit at follow-up whereas patients with a moderate deterioration of MEP showed a stable motor worsening at follow-up in 22% of cases.

D-wave monitoring

D-wave monitorability. After the placement of the extradural electrode, the D-wave was obtained in 185 patients (84.5%). In 129 cases (69,7%) the D-wave showed stability and reproducibility during the procedure and thus the deterioration of its amplitude was adopted as leading IOM parameter throughout the surgical procedure; in 56 cases (30.3%) the D-wave obtained was unstable and not reproducible and thus it was considered not suitable for monitoring ("not monitorable"). In 34 patients (15.5%) it was not inserted as monitoring parameter due to either technical problems or to the fact that tumor location was caudal to T10-T11 ("not monitored").

The univariate analysis showed that the rate of monitorability was influenced by worse preoperative motor status ($p<0.001$), the presence of syrinx rostral or caudal to the tumor ($p=0.01$) and the thoraco-lumbar level ($p=0.006$). The adjusted analysis confirmed the preoperative status as determining factor for D-wave monitorability; more specifically, the risk for unsuccessful D-wave monitoring ("not monitorable") in patients with preoperative McCormick grade of III and IV is respectively of 6 and 23 times higher than patients with McCormick grade I. The presence of syrinx and the thoraco-lumbar level are confirmed as risk factors for not "monitorable" D-wave as well ($p=0.02$ and $p=0.03$ respectively).

D-wave and motor outcome. During surgery, in 127 patients (98.5%) the D-wave amplitude remained above the cutoff of 50% of the baseline amplitude value; on the other hand, in 2 patients (1.5%) the D-wave amplitude at the end of surgery was lower than 50% of the baseline value. Due to the paucity of the second group (D-wave loss or amplitude reduction below the 50% of baseline value) it was not possible to evaluate the relationship between the clinical and neurophysiological data in the opposite group. The comparison of patients with and without a "monitorable" D-wave revealed that at discharge, patients with a preoperative McCormick grade I - II (preoperative grade III and IV are excluded due to the influence on monitorability) and "monitorable" D-wave during surgery showed similar clinical outcome as patients without a "monitorable" D-wave; at follow up, the same group of patients with a "monitorable" D-wave showed a rate of disability (McCormick III-IV) of 6.3% whereas patients without a "monitorable" D-wave presented a rate of disability of 25% ($p=0.002$). A comparison between the whole group of patients with a "monitorable" D-wave and patients with a D-wave not monitored during surgery showed a similar clinical outcome at discharge; at follow-up patients with a monitorable D-wave showed a rate of disability (McCormick III-IV) of 7.5% whereas patients submitted to surgery without D-wave monitoring presented a rate of 26% (p=0.009).

As previously mentioned, the decrease of the D-wave amplitude below 50% of the baseline value was reported in 2 cases. In the first case, the reported McCormick grade at discharge was III (McCormick grade upon admission was II) which remained stable at further follow up (115 months). The D-wave amplitude decrease until 47% of the baseline value and the surgical procedure was initially stopped and finally suspended due to the persistent decrease of the amplitude. The removal of the tumor (pilocitic astrocytoma) was subtotal. In the other case, the D-wave amplitude at the end of surgery was 49% of the baseline values; the patient showed a motor deterioration after surgery (preoperative grade I to postoperative grade III) which ameliorate to grade II at further follow-up (22 months). Both of these cases can be classified as true positive results.

On the other hand, in 2 cases the D-wave remained above the 50% threshold but the patients presented a motor worsening which was stable at follow-up. Both patients were in McCormick grade II upon admission and both presented a McCormick grade III at mean follow-up (90 months). Both these cases can be classified as false negative results (table 2.6).

Table 2.6: Muscle motor evoked potentials (MEPs) changes during surgeries for 125 intramedullary spinal cord tumors (ISCTs) with D-wave amplitude maintained above 50% of the baseline value.

MEP amplitude changes	Number of cases
Stable (no changes from baseline)	56
<50% of baseline value	24
Between 50 and 80% of baseline value	23
>80% of baseline value	22
Complete Loss	2
Total	125

According to our data, the D-wave presented a sensitivity of 33.3%, a specificity of 99.2%, a positive predictive value (PPV) of 50%, a negative predictive value (NPV) of 98.4% and an accuracy of 97.6%.

Discussion

This D-Wave study confirmed its leading role in IOM during surgery for ISCTs. Our results confirmed that at follow-up the whole group of patients with a monitored D-wave presented a better clinical outcome than patients submitted to surgery without a monitorable D-wave. This data confirmed the results obtained earlier by the same surgical team, as described by Sala et al[50] in 2006 in the first study which compared monitored and not monitored ISCTs patients; the authors demonstrated the benefits of IOM during surgery for ISCTs with a significant better outcome at 3 months for IONM patients.

As previously reported, TES MEP are the most appropriate test to monitor the functional integrity of the motor pathways in the short term. Our results confirmed the conclusions of the previous series published by Sala et al[50]; a sudden disappearance of both the D-wave and muscle MEP is very rare and in the present series there was no case of D-wave disappearance. Loss of muscle MEP with stable D-wave should not stop surgery; a step wise check list must be started in order to quickly rule out technical and anesthesiological issues and once other possible sources of muscle MEP deterioration are excluded, then surgery is temporary stopped in order to wait for the MEP amplitude to recover. According to our data, a muscle MEP deterioration > 80% is followed by a new motor deficit with a probability of 75% at the moment of discharge; on the other hand, if the MEP deterioration is between 50% and 80% of the baseline value, the probability of new deficit is 56%. However, at the follow-up evaluation, if the D-wave was maintained above 50% of the baseline value during surgery, it overcomes the reliability of muscle MEP deterioration.

In our series, the D-wave was obtained in 84.5% of cases however it was considered monitorable in 69.7% of cases. Interestingly, we had only two cases of D-wave amplitude reduction below the 50% threshold. We argue that the application of IONM during surgery for ISCTs has indirectly refined the surgical technique. In a 30% of cases the D-wave was considered not monitorable. This condition is often associated to previous surgery[35], radiotherapy[5], preoperative paraplegia[2], large tumor sizes and very young pediatric age, and might also be related to a desynchronization of the D-wave. This theory suggests that, due to either large tumor sizes, syringomyelia, radiotherapy or immaturity of the corticospinal tracts, different axons along the CST conduct the potential volley with different velocities thus resulting in a not synchronous registration at the level of the epidural electrode; as a result, the summation of the potentials is insufficient for obtain a clear and stable D-wave[27].

In our series, the sensitivity reported is 33.3% with a PPV of 50%; however, it should be mentioned that the 2 cases with a motor worsening after surgery with a D-wave maintained above 50% of the baseline value were not neurologically intact upon admission (McCormick grade II) and the deterioration was one grade of the McCormick scale (grade III at follow-up); furthermore, in our series only two patients showed a deterioration of the D-wave below 50% of the baseline value. On the other hand, the specificity reported is very high (99.2%) with a NPV of 98.4%; one should keep in mind that the application of IONM during surgery had taught the surgeons how to take advantage from it and thus how to ameliorate the surgical technique in order to avoid motor sequelae[50,53]. These possibly explains why the number of cases with a D-wave below 50% of the baseline value is very low (2 cases) in this series.

We strongly believe that the application of IONM during surgery for ISCTs is undeniable. Recently, Hadley et al[18] proposed a "guidelines for the use of electrophysiological monitoring for surgery of the human spinal column and spinal cord". In these guidelines, the authors assert that IOM during surgery for ISCTs can be defined as a diagnostic tool instead of a therapeutic adjunct. According to our vision of IOM application in both brain and spinal cord surgery, this conclusion represents a theoretical inaccuracy. The main advantage of IOM during surgery is the capability to alert the surgeon in order to stop surgery before the irreparable damage is done; the ability to predict the permanent motor deficit is clearly useful, but from a surgical point of view is an intraoperative demonstration of a technical failure. Surgeon who support the use of IOM in their daily practice believe in its efficacy to prevent motor injury thus it is difficult to design a Class I randomized trial in order to compare IOM patients vs no IONM patients in their clinical outcome after surgery. The historical control study of Sala et al[50] was designed in order to overcome the ethical concern related to a randomized trial; the authors reported a case matched comparison of patients treated for ISCTs with and without IONM; the final risk ratios (RRs) for IONM cases vs no

IONM cases was 0.27 at 3 months follow-up ($p<0.001$). According to the recently introduced grading of recommendation assessment, development and evaluation (GRADE) spread by Guyatt et al, a flexible rather than rigid hierarchical evidence can be adopted[17]. Furthermore, "... when methodologically strong observational studies yield large or very large and consistent estimates of the magnitude of a treatment effect, we may be more confident about the results."[16] This means that the role of confounding variables falls away with larger effects. Guyatt sets large and very large effect risk ratios (RRs) at <0.5 and <0.2. In this setting, the definition of the evidence class of a clinical study should be reevaluated, especially in conditions in which randomized trial are not ethically feasible.

Conclusion

D-wave monitoring represents a strong predictor of clinical outcome and the clear threshold adopted during surgery helps in the standardization of IONM protocols for ISCTs. According to our data its monitorability is 69.7%; the specificity is 99.2%, the NPV is 98.4% and the accuracy is 97.6%.

SECTION 3: NEW INSIGHT DURING SURGERY FOR BRAIN TUMORS IN MOTOR AREAS: THE APPLICATION OF D-WAVE MONITORING. EARLY RESULTS.

Background

According to the limitations of muscle MEPs in predicting motor outcome after brain surgery, the introduction of a more reliable IOM marker for motor prediction is desirable. Therefore, in the light of the confirmed high reliability of D-wave monitoring in ISCT surgery, we decided to apply the D-wave monitoring during surgery for tumors located in motor areas. The fewer experience reported in the literature[11,12,60] are related mainly to the necessity to insert the epidural electrode along the cervical spine with a percutaneous technique, thus adding an additional risk to the surgical procedure itself. However, the technical procedure for inserting the electrode is a standard practice during neurosurgical procedure for neuromodulation[7-9]. Yamamoto et al[60] were the first who evaluated the application of D-wave monitoring for brain surgery in motor areas. The authors divided the 37 patients in 4 groups according to the tumor location (premotor area, supplementary motor area, M1 and somatosensory area) and they described a higher rate of D-wave decrease below 30% of the baseline amplitude for tumor located in M1; furthermore, the amplitude decrease below the 30% threshold was related to a permanent postoperative in all cases. Fujiki et al[11] compared the MEP recorded from muscles with the cortico spinal evoked potentials (D and I waves); in this study, patients are classified according to different deterioration of the evoked potentials during surgery. The authors reported a correlation between the variation of muscle MEP and the I waves. Furthermore, the authors underlined that a decrease of muscle MEP with a stable D-wave during surgery is not followed by permanent deficit after surgery; on the other hand, a decrease of the D-wave below 30% of the original value (together with a muscle MEP and I-wave decrease) is always related with permanent postoperative deficits. Fukaya et al[12] evaluated the characteristics of the D-wave obtained through subcortical stimulation and they described a “subcortical D-wave” with similar characteristics as the D-wave obtained through cortical stimulation, but with a shorter latency.

In this section, we describe our preliminary results with the application of D-wave monitoring during surgery for brain tumors in motor area.

Methods

Between 2016 and 2017 we had the opportunity to attempt D-wave monitoring during intracranial surgery in three patients with brain lesions.

Clinical evaluation and preoperative assessment

Patients are evaluated according to the MRC scale at admission, after surgery, at discharge and at follow-up (see Section 1, Methods - *Patients' population and preoperative assessment* for further details about clinical evaluation and classification of neurological deterioration).

All of the patients underwent MRI for diagnosis and localization of the tumor together with DTI fiber tracking of the CST; the data collected were used for intraoperative neuro-navigation (see Section 1 - *Methods*).

Anesthesia protocol

Total intravenous anesthesia protocol adopted was the same as in section 1 (see Section 1, Methods).

Intraoperative monitoring and warning criteria - D-wave monitoring

The setting adopted for muscle MEP monitoring is reported in detail in the first section - Methods. TES for D-wave recording was performed as described previously for ISCT surgery.

The epidural electrode required for D-wave recordings was inserted in the epidural cervical space with a percutaneous technique before the beginning of the surgical procedure. The patient was placed

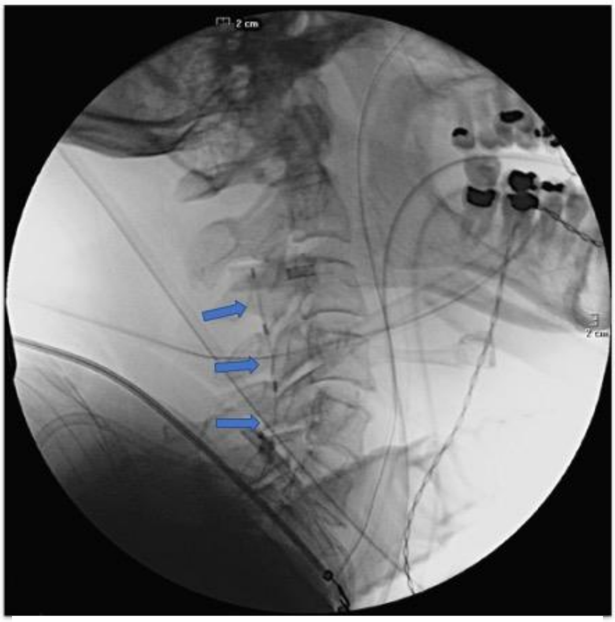


Figure 3.1. Cervical latero-lateral fluoroscopic visualization (arrows) of the epidural electrode location with the distal tip at C2-C3 level.

in prone position under general anesthesia; with the aid of fluoroscopic guidance a Tuohy needle (18 gauge) was inserted in the midline epidural space at the cervical-thoracic junction. The correct placement of the needle in the epidural space was confirmed from the change of resistance observed after injection of saline solution through the needle. The electrode was then inserted through the needle and then advanced upwards along the epidural cervical space, up to the C3 level; once the electrode position was verified with fluoroscopy in lateral projection (Figure 3.1), the Tuohy needle is removed and the electrode is fixed with adhesive tape and sutures on the skin in order to avoid displacement during the final positioning of the patient. The stimuli were applied as monophasic square-wave pulse of 0.2-0.5 msec duration delivered at 2 Hz. As for MEP monitoring, D-wave was initially elicitated by TES via corkscrew needle electrodes on the scalp then, once the surgical field was exposed, it was elicited by direct cortical or subcortical stimulation. The signal recorded was filtered with with a bandpass range of 5 Hz to 5k Hz using the same instrumentation adopted in Section 1 and 2 (see Section 1 - *Methods)*.

Patient 1

A 52 y/o man with a previous history of non-small cells lung cancer (NSCLC) was referred to our Institute due to the regrowth of a previously treated frontal precentral metastasis (surgical removal followed by radiotherapy and chemotherapy one year before). One month before admission, a total-body CT scan revealed a slight reduction of the primary lung tumor's volume together with a reduction of the loco-regional lymphadenopathy. Preoperative MRI showed a left precentral tumor with diffuse and irregular contrast enhancement (fig. 3.2); DTI fiber tracking with CST reconstruction was also performed. The physical examination upon admission revealed a severe right hemiparesis (mean MRC =2) especially at the leg and mild cognitive impairment. The patient was scheduled for surgical removal of the tumor with the aid of IOM and D-wave monitoring. Informed consents were collected for the surgical procedure and for the placement of the cervical epidural electrode.

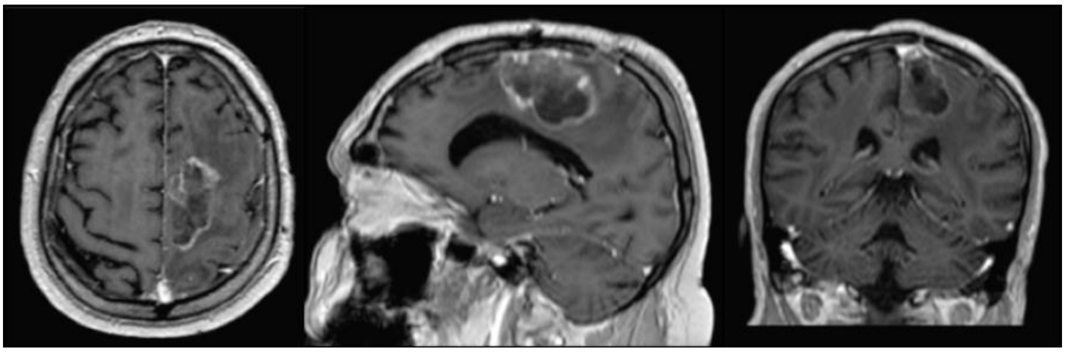


Figure 3.2. Preoperative axial, sagittal and coronal T1 weighted contrast enhanced MRI scan showing a left mesial precentral tumor.

The day of surgery after the insertion of the epidural electrode, the patient was positioned supine with the head in neutral position and flexed 30° ventrally; thorax and abdomen were gently flexed together with the legs that were positioned slightly flexed with cushions placed under the knees. After patient positioning, baseline TES MEP were recoded together with the D-wave. Interestingly, we were able to record the D-wave only when the right hemisphere was stimulated, whereas no D-wave was recorded when the left hemisphere was stimulated (fig. 3.3). The TES D-wave recording from the right hemisphere was not repeated during the procedure. We did not obtain the D-wave from DCS.

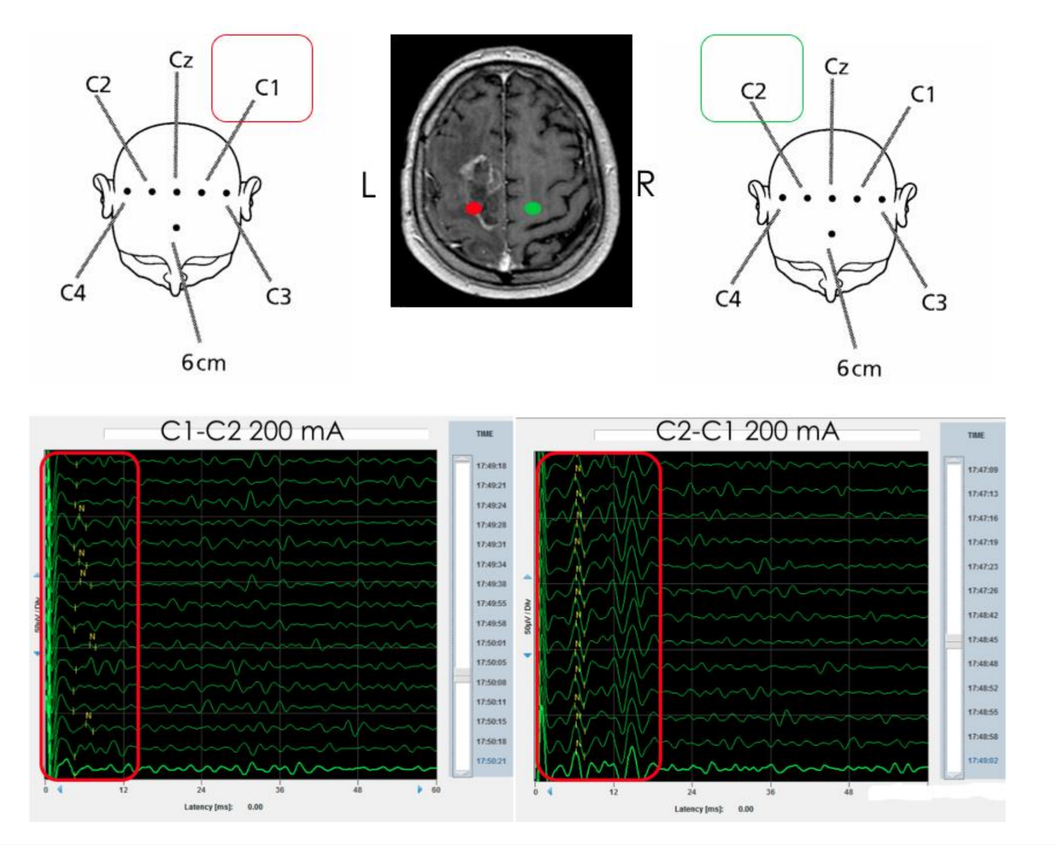


Figure 3.3. Schematic representation of the TES method applied for the stimulation of the left (left panels) and right hemispheres (right panels); after the TES stimuli on the same side of the tumor (left panels) no clear D-wave was recorded (left red rectangle, lower left panel); TES stimuli on the opposite side produce a visible D-wave (right red rectangle, lower right panel).

During surgery, muscle MEP monitoring did not show any significant modification. At the end of the surgical procedure, a lateral fluoroscopy of the cervical spine was done in order to rule out any possible change of the original position of the epidural electrode. Interestingly, the electrode was localized outside of the spinal canal, at the level of the lamina and spinose of C5 (figure 3.4). There were no complications related to the epidural electrode.

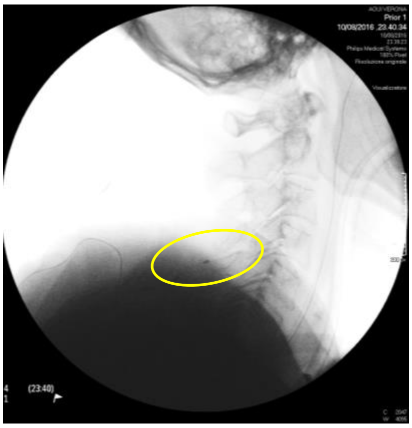


Figure 3.4. Misplacement of the electrode at the end of surgery (yellow circle).

After surgery, the patient a stable right hemiparesis (arm mean MRC 2/5 and leg mean MRC 1/5). At discharge, the patient presented no motor-cognitive slowing and showed an amelioration of the arm paresis (mean MRC 3/5). Postoperative MRI showed complete removal of the tumor (see figure 3.5). At 3 months follow-up, the patient presented a further amelioration of the hemiparesis (mean MRC 4/5 for the upper left limb, 3/5 for the lower left limb). Pathology confirmed the lung origin of the metastatic tumor.

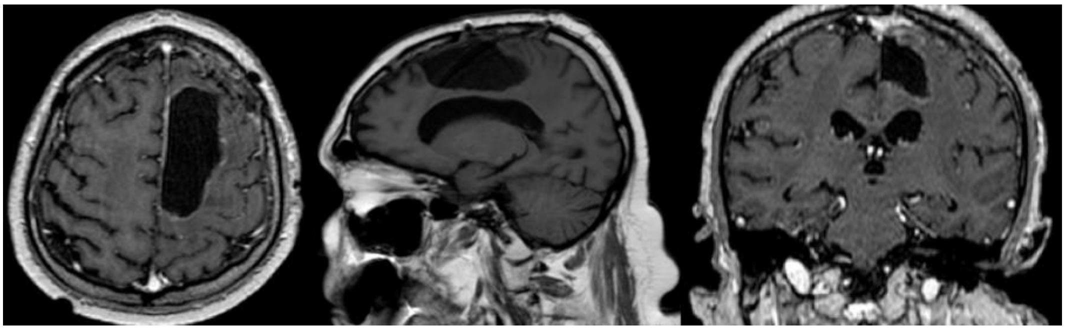


Figure 3.5. Postoperative T1 weighted contrast enhanced axial, sagittal and coronal MRI images showing a complete removal of the tumor.

Patient 2

A 62 y/o man, left-handed, was referred to the emergency room and then to our Institute due to the gradual onset of dysphasia and left arm numbness during the last week before admission. The physical examination upon admission showed severe paresis of the left arm, especially at distal segments (mean MRC 2). An MRI scan revealed a 5cm max diameter intra-axial cystic tumor located in the frontal precentral lobule; the tumor showed a marginal contrast enhancement. During the same study, DTI fiber tracking was applied for the reconstruction of the CST and arcuate fasciculus (see figure 3.6). The patient was scheduled for surgical removal of the tumor with the aid of IOM and D-wave monitoring. Informed consents were collected for the surgical procedure and for the placement of cervical epidural electrode.

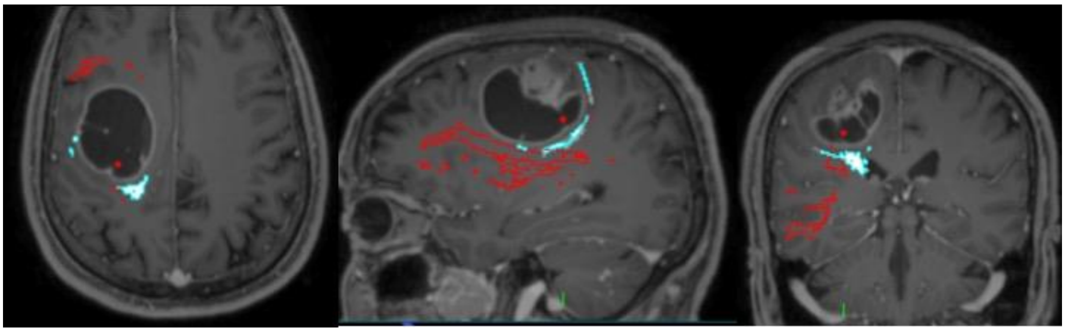


Figure 3.6. Preoperative MRI scan: axial, sagittal and coronal T1-weighted contrast enhanced images revealed a precentral tumor, partially cystic with a posterior-superior nodule close to M1. DTI fiber tracking defined the CST (blue) and the arcuate fasciculus (red).

The day of surgery after the insertion of the epidural electrode, the patient positioning was the same as for Case 1. After patient positioning, TES MEP were recoded together with the D-wave. A frontal craniotomy was then performed with the exposure of the frontal - M1 area; the tumor was not visible at the surface. The phase-reversal was attempted for the

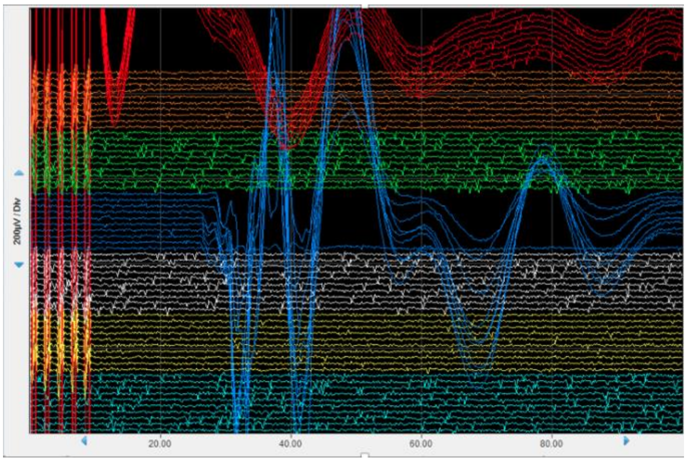


Figure 3.7. Cortical mapping of the peri-tumoral motor cortex with response from the left abductor pollicis brevis muscle (blue) at 10mA. The deflection of the red traces in the upper part of the panel is a stimulus related artifact due to the proximity of the stimulating probe to the recording electrode (orbicularis ori).

identification of the central sulcus, but the results were not successful thus a cortical mapping with monopolar probe at different threshold was started (see figure 3.7). Data provided by cortical stimulation revealed that the tumor was located anteriorly to M1 which was displaced posteriorly. Muscle MEP recordings and monitoring was obtained through DCS, however it was not possible to obtain a clear D-wave with the same stimulation method.

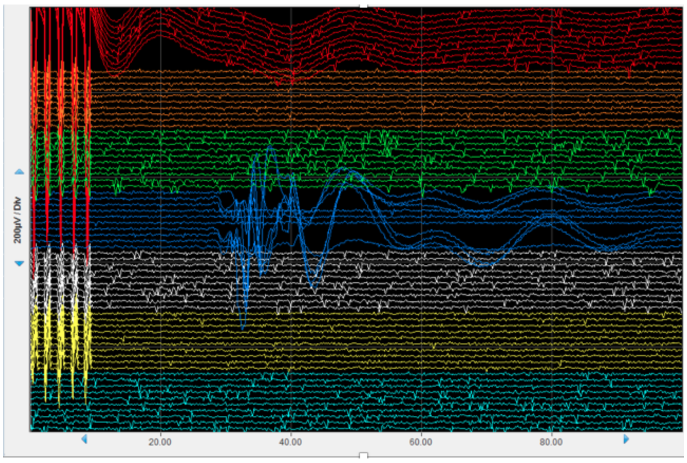


Figure 3.8. Subcortical mapping along the CST with wide response from the left abductor pollicis brevis muscle (blue) at 2mA. The deflection of the red traces in the upper part of the panel is a stimulus related artifact due to the proximity of the stimulating probe to the recording electrode (orbicularis ori).

During the surgical resection, subcortical mapping was performed along the CST with a monopolar probe (range of stimulation 2mA to 20mA) with clear response from the upper and legs; a clear response from the left arm was obtained at 2mA (see figure 3.8). The surgical field along the CST was mapped also with a bipolar probe in order to obtain the D-wave: a clear response (subcortical D-wave) was obtained in different areas with a range of stimulation between 5mA and 20mA (see figure 3.9). At the end of surgery, muscle MEP were stable. There were no complications related to the epidural electrode. The position of the electrode was not checked at the end of surgery.

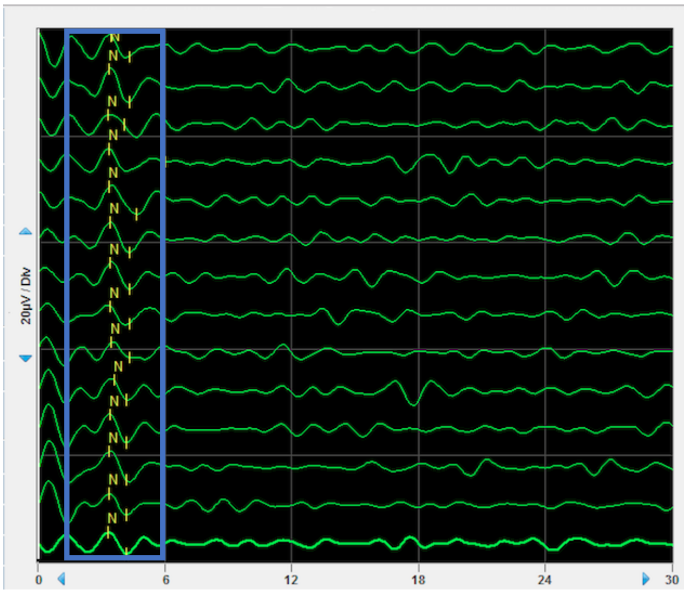


Figure 3.9. Subcortical mapping along the CST with bipolar probe obtaining a clear D-wave from the cervical epidural electrode at 5mA (blue rectangle).

After surgery, the patient was recovered in the ICU for a gradual weakening from the general anesthesia; postoperative MRI showed complete removal of the tumor (see figure 3.10). The patient showed a slight amelioration of the left arm paresis which remained stable at discharge. Three months after surgery the patient showed a clear amelioration of the left arm paresis (mean MRC 4). The analysis of the specimens revealed a glioblastoma multiforme.

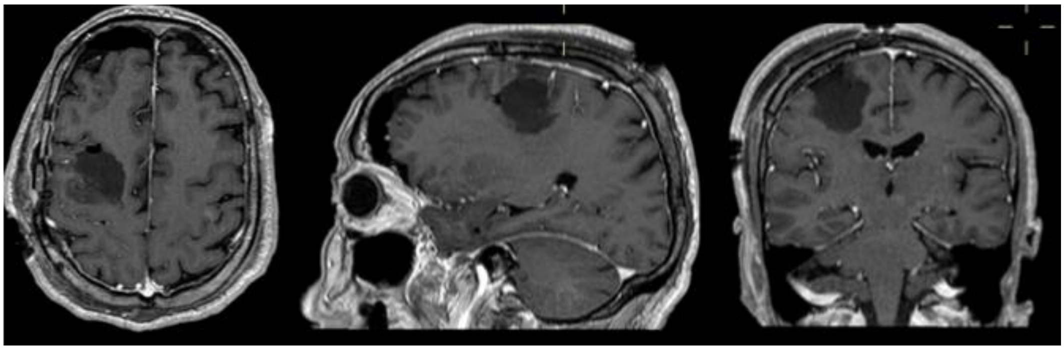


Figure 3.10. Postoperative MRI: axial, sagittal and coronal T1 weighted contrast-enhanced images showing complete removal of the tumor.

Patient 3

A 48 y/o man with a recent history of right hemicolectomy for adenocarcinoma was referred to our Institute due the gradual onset of a right hemiparesis related to the presence of a left precentral subcortical tumor. An MRI confirmed the presence of a single left precentral metastasis, adherent to the CST which was reconstructed with the aid of DTI fiber tracking (see figure 3.11). The physical examination upon admission revealed a mild right hemiparesis (mean MRC 4). The patient was scheduled for surgical removal of the tumor with the aid of IONM and D-wave monitoring. Informed consents were collected for the surgical procedure and for the placement of cervical epidural electrode.

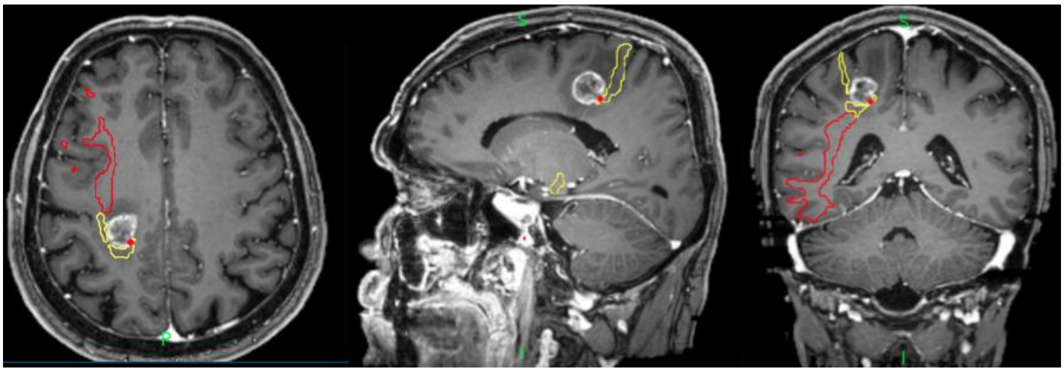


Figure 3.11. Preoperative MRI scan: axial, sagittal and coronal T1-weighted contrast enhanced images revealed a left subcortical precentral tumor; DTI fiber tracking was applied for the reconstruction of the CST (yellow) and of the arcuate fasciculus (red).

The day of surgery after the insertion of the epidural electrode, the patient was positioned in the same way as cases 1 and 2. After patient positioning, TES MEP were recoded together with the D-wave. It was not possible to obtain the D-wave from DCS. Cortical mapping with monopolar technique generated response from the left brachial biceps, the extensor digitorum longus and the abductor pollicis brevis (range of stimulation 2mA-7mA). An attempt to record the D-wave from cortical stimulation was unsuccessful. The resection of the tumor proceeded without significant deterioration of the muscle MEP. Subcortical mapping along the CST was possible at 3 mA with response recorded from the abductor pollicis brevis.

Bipolar subcortical stimulation along the CST at 15mA produced a clear D-wave (see figure 3.12).

After surgery, the patient did not show any significant clinical deterioration of the physical examination. There were no complications related to the epidural electrode. The position of the electrode was not checked at the end of surgery.

A postoperative contrast-enhanced CT scan revealed a complete removal of the tumor. Upon discharge, the lower left limb paresis was disappeared; the arm paresis was still present (mean MRC 4). One month after surgery the deficit was completely resolved. Pathology confirmed the colon origin of the metastatic tumor.

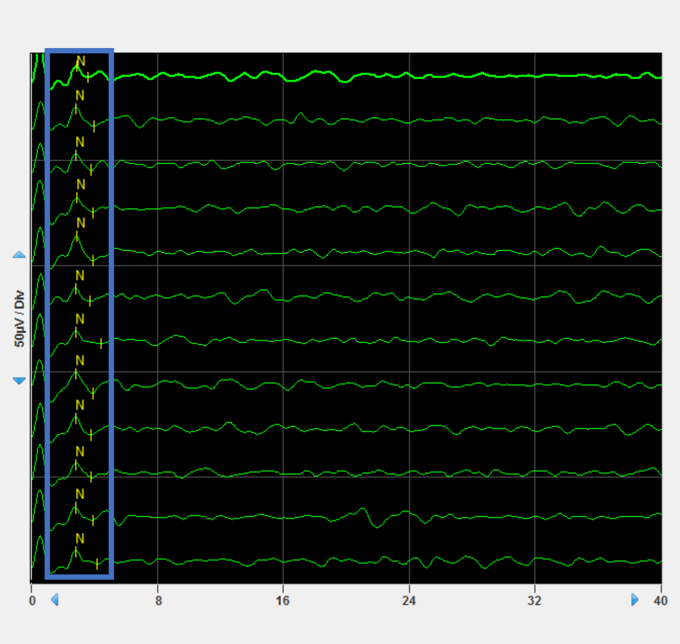


Figure 3.12. Bipolar subcortical stimulation along the CST produced a clear D-wave (blue rectangle).

Discussion

Surgical removal of tumors located in motor areas remains a challenge in terms of both surgical technique and direct interpretation of MEP changes during the removal of the tumor. As highlighted in the first section, intraoperative changes of muscle MEP are multifactorial and not always clearly related with the surgical outcome[36]. Furthermore, different influencing factors can alter the correct interpretation of the data making fast decision even more difficult. In order to overcome the limitations of muscle MEP variability, the introduction of a strong outcome predictor as D-wave, is therefore advisable.

The first step that one has to face for the application of D-wave monitoring during brain surgery is the placement of the epidural cervical electrode. Even if the percutaneous technique is somewhat standardized during neuromodulation procedures[7-9], it is undeniable that its application rises the risk of the whole surgical procedure itself. Possible complications due to the placement of the electrode are wound infection, cerebrospinal fluid leaks, dural puncture headaches, epidural hematoma and spinal cord trauma. Infection is the most common procedural complication with a reported incidence of 1.4% to 11%[15], however in the literature this range of incidence is related to the placement of permanent spinal cord stimulation device. The group of Yamamoto et al[60] reported in different publications over 200 cases of cervical epidural electrode placement without significant clinical complications[22-24,59]. In our cases, we did not experience any complication related to the placement of the extradural cervical electrode. Interestingly, in our first case, we were able to obtain the D-wave with TES with a suboptimal placement of the electrode (figure 3.4). In this case, we verified the position of the electrode only during the placement in prone position and at the end of surgery (in supine position). We argued that the misplacement of the electrode occurred during the positioning of the patient from prone to supine position; accordingly, in the other two cases, we verified the electrode position before and at the end of surgery. The scenario opened with this observation needs further investigations in order to prove the efficacy of D-wave monitoring with a different placement of the electrode. As a matter of fact, one could argue that the migration of the electrode can lead to a misinterpretation of the D-wave changes. In this setting, a comparison between the D-waves recorded during surgery for ISCTs with different placement of the electrode might be useful. If the value of D-wave recorded from outside the spinal canal will be confirmed, then the risk of invasive placement of the electrode can be eliminated.

The usefulness of D-wave monitoring during surgery in motor areas become critical if an intermediate MEP amplitude deterioration occurred: as reported by Fujiki et al[11], patients who experienced an MEP amplitude deterioration without D-wave changes (group C) experienced a transient motor deficit after surgery; on the other hand, MEP loss was always related with a D-wave significant reduction (mean decrease 39.5%) and with stable motor deficits (group D). The difference between these two groups was related to the extent of damage at the level of the surgical field: MEP loss represent an irreversible damage of the motor system and as stated by Fujiki et al[11] this can be attributed to a damage of the subcortical pyramidal fibers. On the other hand, a MEP deterioration is the expression of a cortical gray matter damage, mostly related to interneuron dysfunction. In such a condition, the D-wave is maintained unchanged: as demonstrated in experimental settings, the D-wave survives after the removal of the cortical gray matter and therefore it is thought to originate from the stimulation of the corticospinal axons in the subcortical white matter[43]. In the case 2 and 3 it was possible to obtain a D-wave after subcortical stimulation of the CST with a bipolar probe. Differently from Fukaya et al[12], we did not found any technical problem in the subcortical D-wave elicitation with the bipolar probe. As previously reported, the bipolar probe evokes only immediately activation of the cortex without spreading of current[19]. However, as demonstrated by the subcortical mapping in which we were able to map the CST at 2mA in both cases 2 and 3, due to the fact that we worked very close to the CST it is likely that this can explain the reason why we had no difficulties with bipolar probe D-wave elicitation. It should be mentioned that, during subcortical mapping, we trusted only the standard monopolar technique for the definition of the CST proximity. The elicitation of the D-wave with bipolar subcortical stimulation was done at the end of the surgical resection in patient 2 and 3; therefore, we cannot draw conclusions on its ability to help in the localization of the CST and, above all, its proximity to the surgical field.

In all the three cases, it was not possible to obtain a D-wave from DCS. In the first patient, it was possible to obtain the D-wave from contralateral hemisphere TES technique, but not from the ipsilateral; conversely, in cases 2 and 3 we obtained an ipsilateral D-wave with TES technique. The reason for this difference can be related to the preoperative clinical and radiological features of the three patients: in case 1, the tumor was cortical-subcortical located whereas in cases 2 and 3 both tumors were only subcortical; the patient 1 was submitted to surgery with a severe hemiparesis, whereas the other two patients presented in a better preoperative clinical condition. In patient 1, it was possible to record muscle MEP from only one muscle at 20 mA with an amplitude of 70μV. In patients 2 and 3, we obtained muscle MEPs and D-wave from TES and only muscle MEPs from DCS. This may be due to a desynchronization of the D-wave secondary to the derangements of the CST at the cortical/subcortical border, due to the presence of the tumor. More specifically, patients 2 and 3 presented a subcortical tumor (figg. 3.6 and 3.11) located along the CST; the deeper stimulation produced by TES could have bypassed the tumor producing a deeper stimulation of the axons allowing the recording of the D-wave. One could also argue that the position of the DCS electrode was not over M1, however all these surgeries were done with the aid of neuronavigation: the position of the surface electrode was verified immediately after its placement over the brain surface. More specifically, patients 2 and 3 showed an intact brain surface allowing us to precisely verified M1 at the beginning of surgery with the aid of neuronavigation; then, the surface electrode was positioned and M1 location was further verified with the phase-reversal technique in both case followed by direct cortical mapping.

Summary conclusion

IOM is a valuable help in the daily practice of neurosurgery. Its application during brain and spinal cord surgery is getting wider and wider over the years. Brain surgery in motor areas remains a classical indication for IOM, however as outlined before, clearer thresholds and stronger outcome predictors are required in order to gain the capability of IOM to prevent rather than to predict the new onset of motor deficits.

As outlined in the first section of this thesis, muscle MEP monitoring during surgery in motor areas is influenced by multiple pre- and intra-operative factors that complicate the intraoperative “on line” interpretation of the data; a stronger outcome predictor is therefore advisable. In the second section our results confirmed the reliability of D-wave monitoring during surgery for ISCTs; if the D-wave amplitude is maintained above 50% of the baseline value throughout the surgical procedure the risk of postoperative long-term deficit is negligible.

The application of D-wave monitoring during surgery in motor areas is a promising technique, especially due to the strong value of the D-wave in the prediction of long term clinical outcome. Due to the small sample size of our cases with monitored D-wave during brain surgery it is impossible to generalize. However, it is worthy to further investigate the role of the position of the epidural electrode in the quality of D-wave monitoring and it is useful to highlight that we did not experienced any complication related to the percutaneous insertion of the cervical electrode. We need to proceed in the enrollment of patient for D-wave monitoring during brain surgery in order to better evaluate the relationship between clinical outcome and D-wave changes during surgery together with the deterioration of muscle MEP amplitude.

References

1. Ammirati M, Vick N, Liao YL, Ciric I, Mikhael M: Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. **Neurosurgery 21:**201-206, 1987

2. Boyd SG, Rothwell JC, Cowan JM, Webb PJ, Morley T, Asselman P, et al: A method of monitoring function in corticospinal pathways during scoliosis surgery with a note on motor conduction velocities. **J Neurol Neurosurg Psychiatry 49:**251-257, 1986

3. Cedzich C, Taniguchi M, Schafer S, Schramm J: Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. **Neurosurgery 38:**962-970, 1996

4. Council MR: Aids to examination of the peripheral nervous system. **Memorandum no 45: Her Majesty's Stationary Office**, 1976

5. de Scisciolo G, Bartelli M, Magrini S, Biti GP, Guidi L, Pinto F: Long-term nervous system damage from radiation of the spinal cord: an electrophysiological study. **J Neurol 238:**9-15, 1991

6. Deletis V, Sala F: Intraoperative neurophysiological monitoring of the spinal cord during spinal cord and spine surgery: a review focus on the corticospinal tracts. **Clin Neurophysiol 119:**248-264, 2008

7. Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Meglio M, et al: Direct recording of the output of the motor cortex produced by transcranial magnetic stimulation in a patient with cerebral cortex atrophy. **Clin Neurophysiol 115:**112-115, 2004

8. Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Meglio M, et al: Comparison of descending volleys evoked by transcranial and epidural motor cortex stimulation in a conscious patient with bulbar pain. **Clin Neurophysiol 115:**834-838, 2004

9. Di Lazzaro V, Oliviero A, Profice P, Meglio M, Cioni B, Tonali P, et al: Descending spinal cord volleys evoked by transcranial magnetic and electrical stimulation of the motor cortex leg area in conscious humans. **J Physiol 537:**1047-1058, 2001

10. Forster MT, Marquardt G, Seifert V, Szelenyi A: Spinal cord tumor surgery--importance of continuous intraoperative neurophysiological monitoring after tumor resection. **Spine (Phila Pa 1976) 37:**E1001-1008, 2012

11. Fujiki M, Furukawa Y, Kamida T, Anan M, Inoue R, Abe T, et al: Intraoperative corticomuscular motor evoked potentials for evaluation of motor function: a comparison with corticospinal D and I waves. **J Neurosurg 104:**85-92, 2006

12. Fukaya C, Sumi K, Otaka T, Shijo K, Nagaoaka T, Kobayashi K, et al: Corticospinal descending direct wave elicited by subcortical stimulation. **J Clin Neurophysiol 28:**297-301, 2011

13. Ghadirpour R, Nasi D, Iaccarino C, Giraldi D, Sabadini R, Motti L, et al: Intraoperative neurophysiological monitoring for intradural extramedullary tumors: why not? **Clin Neurol Neurosurg 130:**140-149, 2015

14. Gossl C, Fahrmeir L, Putz B, Auer LM, Auer DP: Fiber tracking from DTI using linear state space models: detectability of the pyramidal tract. **Neuroimage 16:**378-388, 2002

15. Grabow TS, Tella PK, Raja SN: Spinal cord stimulation for complex regional pain syndrome: an evidence-based medicine review of the literature. **Clin J Pain 19:**371-383, 2003

16. Guyatt GH, Cook DJ, Jaeschke R, Pauker SG, Schunemann HJ: Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). **Chest 133:**123s-131s, 2008

17. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al: GRADE guidelines: 9. Rating up the quality of evidence. **J Clin Epidemiol 64:**1311-1316, 2011

18. Hadley MN, Shank CD, Rozzelle CJ, Walters BC: Guidelines for the Use of Electrophysiological Monitoring for Surgery of the Human Spinal Column and Spinal Cord. **Neurosurgery 81:**713-732, 2017

19. Haglund MM, Ojemann GA, Blasdel GG: Optical imaging of bipolar cortical stimulation. **J Neurosurg 78:**785-793, 1993

20. He SQ, Dum RP, Strick PL: Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. **J Neurosci 15:**3284-3306, 1995

21. Hill AB: THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? **Proc R Soc Med 58:**295-300, 1965

22. Katayama Y: Assessment of spinal cord injury with multimodality evoked spinal cord potentials. Part 1. Localization of lesions in experimental spinal cord injury. **Neuro-orthopedics 1:**130-141, 1986

23. Katayama Y, Tsubokawa T, Hirayama T, Himi K, Koyama S, Yamamoto T: Embolization of intramedullary spinal arteriovenous malformation fed by the anterior spinal artery with monitoring of the corticospinal motor evoked potential--case report. **Neurol Med Chir (Tokyo) 31:**401-405, 1991

24. Katayama Y, Tsubokawa T, Maejima S, Hirayama T, Yamamoto T: Corticospinal direct response in humans: identification of the motor cortex during intracranial surgery under general anaesthesia. **J Neurol Neurosurg Psychiatry 51:**50-59, 1988

25. Kombos T, Picht T, Derdilopoulos A, Suess O: Impact of intraoperative neurophysiological monitoring on surgery of high-grade gliomas. **J Clin Neurophysiol 26:**422-425, 2009

26. Kombos T, Suess O, Ciklatekerlio O, Brock M: Monitoring of intraoperative motor evoked potentials to increase the safety of surgery in and around the motor cortex. **J Neurosurg 95:**608-614, 2001

27. Kothbauer K, Deletis V, Epstein FJ: Intraoperative spinal cord monitoring for intramedullary surgery: an essential adjunct. **Pediatr Neurosurg 26:**247-254, 1997

28. Kothbauer KF, Deletis V, Epstein FJ: Motor-evoked potential monitoring for intramedullary spinal cord tumor surgery: correlation of clinical and neurophysiological data in a series of 100 consecutive procedures. **Neurosurg Focus 4:**e1, 1998

29. Krieg SM, Schaffner M, Shiban E, Droese D, Obermuller T, Gempt J, et al: Reliability of intraoperative neurophysiological monitoring using motor evoked potentials during resection of metastases in motor-eloquent brain regions: clinical article. **J Neurosurg 118:**1269-1278, 2013

30. 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 70:**1060-1070; discussion 1070-1061, 2012

31. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al: The 2007 WHO classification of tumours of the central nervous system. **Acta Neuropathol 114:**97-109, 2007

32. Luppino G, Matelli M, Camarda R, Rizzolatti G: Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. **J Comp Neurol 338:**114-140, 1993

33. Luppino G, Rizzolatti G: The Organization of the Frontal Motor Cortex. **News Physiol Sci 15:**219-224, 2000

34. Macdonald DB, Skinner S, Shils J, Yingling C: Intraoperative motor evoked potential monitoring - a position statement by the American Society of Neurophysiological Monitoring. **Clin Neurophysiol 124:**2291-2316, 2013

35. Morota N, Deletis V, Constantini S, Kofler M, Cohen H, Epstein FJ: The role of motor evoked potentials during surgery for intramedullary spinal cord tumors. **Neurosurgery 41:**1327-1336, 1997

36. Neuloh G, Pechstein U, Cedzich C, Schramm J: Motor evoked potential monitoring with supratentorial surgery. **Neurosurgery 54:**1061-1070; discussion 1070-1062, 2004

37. Neuloh G, Pechstein U, Schramm J: Motor tract monitoring during insular glioma surgery. **J Neurosurg 106:**582-592, 2007

38. Neuloh G, Schramm J: Are there false-negative results of motor evoked potential monitoring in brain surgery? **Cent Eur Neurosurg 70:**171-175, 2009

39. Neuloh G, Schramm J: Monitoring of motor evoked potentials compared with somatosensory evoked potentials and microvascular Doppler ultrasonography in cerebral aneurysm surgery. **J Neurosurg 100:**389-399, 2004

40. Nitta T, Sato K: Prognostic implications of the extent of surgical resection in patients with intracranial malignant gliomas. **Cancer 75:**2727-2731, 1995

41. 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 114:**738-746, 2011

42. Obermueller T, Schaeffner M, Shiban E, Droese D, Negwer C, Meyer B, et al: Intraoperative neuromonitoring for function-guided resection differs for supratentorial motor eloquent gliomas and metastases. **BMC Neurol 15:**211, 2015

43. Patton HD, Amassian VE: Single and multiple-unit analysis of cortical stage of pyramidal tract activation. **J Neurophysiol 17:**345-363, 1954

44. Penfield W, Welch K: The supplementary motor area of the cerebral cortex; a clinical and experimental study. **AMA Arch Neurol Psychiatry 66:**289-317, 1951

45. Reinges MH, Nguyen HH, Krings T, Hutter BO, Rohde V, Gilsbach JM: Course of brain shift during microsurgical resection of supratentorial cerebral lesions: limits of conventional neuronavigation. **Acta Neurochir (Wien) 146:**369-377; discussion 377, 2004

46. Ringel F, Sala F: Intraoperative mapping and monitoring in supratentorial tumor surgery. **J Neurosurg Sci 59:**129-139, 2015

47. Rizzolatti G, Luppino G: The cortical motor system. **Neuron 31:**889-901, 2001

48. Sala F, Bricolo A, Faccioli F, Lanteri P, Gerosa M: Surgery for intramedullary spinal cord tumors: the role of intraoperative (neurophysiological) monitoring. **Eur Spine J 16 Suppl 2:**S130-139, 2007

49. Sala F, Lanteri P: Brain surgery in motor areas: the invaluable assistance of intraoperative neurophysiological monitoring. **J Neurosurg Sci 47:**79-88, 2003

50. Sala F, Palandri G, Basso E, Lanteri P, Deletis V, Faccioli F, et al: Motor evoked potential monitoring improves outcome after surgery for intramedullary spinal cord tumors: a historical control study. **Neurosurgery 58:**1129-1143; discussion 1129-1143, 2006

51. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS: An extent of resection threshold for newly diagnosed glioblastomas. **J Neurosurg 115:**3-8, 2011

52. Scerrati M, Roselli R, Iacoangeli M, Pompucci A, Rossi GF: Prognostic factors in low grade (WHO grade II) gliomas of the cerebral hemispheres: the role of surgery. **J Neurol Neurosurg Psychiatry 61:**291-296, 1996

53. Scibilia A, Terranova C, Rizzo V, Raffa G, Morelli A, Esposito F, et al: Intraoperative neurophysiological mapping and monitoring in spinal tumor surgery: sirens or indispensable tools? **Neurosurg Focus 41:**E18, 2016

54. Seidel K, Beck J, Stieglitz L, Schucht P, Raabe A: The warning-sign hierarchy between quantitative subcortical motor mapping and continuous motor evoked potential monitoring during resection of supratentorial brain tumors. **J Neurosurg 118:**287-296, 2013

55. Skinner SA, Holdefer RN: Intraoperative neuromonitoring alerts that reverse with intervention: treatment paradox and what to do about it. **J Clin Neurophysiol 31:**118-126, 2014

56. Szelenyi A, Hattingen E, Weidauer S, Seifert V, Ziemann U: Intraoperative motor evoked potential alteration in intracranial tumor surgery and its relation to signal alteration in postoperative magnetic resonance imaging. **Neurosurgery 67:**302-313, 2010

57. Szelenyi A, Langer D, Kothbauer K, De Camargo AB, Flamm ES, Deletis V: Monitoring of muscle motor evoked potentials during cerebral aneurysm surgery: intraoperative changes and postoperative outcome. **J Neurosurg 105:**675-681, 2006

58. Taniguchi M, Cedzich C, Schramm J: Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. **Neurosurgery 32:**219-226, 1993

59. Tsubokawa T: Clinical application of corticospinal evoked potentials as a monitor of pyramidal function. **Nihon Univ J Med 28:**27-37, 1986

60. Yamamoto T, Katayama Y, Nagaoka T, Kobayashi K, Fukaya C: Intraoperative monitoring of the corticospinal motor evoked potential (D-wave): clinical index for postoperative motor function and functional recovery. **Neurol Med Chir (Tokyo) 44:**170-180; discussion 181-172, 2004

61. Yordanova YN, Moritz-Gasser S, Duffau H: Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article. **J Neurosurg 115:**232-239, 2011

62. Yousry TA, Schmid UD, Schmidt D, Hagen T, Jassoy A, Reiser MF: The central sulcal vein: a landmark for identification of the central sulcus using functional magnetic resonance imaging. **J Neurosurg 85:**608-617, 1996