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Maastricht University

Faculty of Medicine and Life Sciences
School for Life Sciences
Master of Biomedical Sciences

Masterthesis

Prospective and retrospective data collection to optimize the use of multimodal intraoperative neuromonitoring

Ans Claesen

Thesis presented in fulfillment of the requirements for the degree of Master of Biomedical Sciences, specialization Clinical Molecular Sciences

SUPERVISOR :
Prof. Dr. Frank WEYNS
Prof. dr. Ivo LAMBRICHTS

MENTOR :
dr. Ludovic ERNON

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Content

Abbreviations

5-ALA	5-aminolevulinic acid
BAEP	Brainstem auditory evoked potentials
BIC	Bayesian information criterion
BOLD	Blood oxygenation level-dependent
CMAP	Compound muscle action potentials
CN	Cranial nerve
CPA	Cerebellopontine angle
CST	Corticospinal tract
DCS	Direct cortical stimulation
DLBCL	Diffuse large B-cell lymphoma
dMEP	Direct motor evoked potential
DSCS	Direct subcortical stimulation
DTI	Diffusion tensor imaging
D-wave	Direct-wave
ECoG	Electrocorticography
EEG	Electroencephalography
EMG	Electromyography
EP	Evoked potential
fMRI	Functional magnetic resonance imaging
FN	Facial nerve
IONM	Intraoperative neuromonitoring
ISI	Interstimulus interval
LMN	Lower motor neuron
MAC	Mean alveolar concentration
MEP	Motor evoked potential
mMEP	Muscle motor evoked potential
MRC	Medical Research Council
N_2O	Nitrous oxide
PMC	Primary motor cortex
QoL	Quality of life
sMRC	Simplified Medical Research Council
SSEP	Somatosensory evoked potential
TES	Transcranial electric stimulation
TIVA	Total intravenous anesthetic
tMEP	Transcranial motor evoked potential
TMS	Transcranial magnetic stimulation
VEP	Visual evoked potential
VPL	Ventral posterolateral nucleus
ZOL	Ziekenhuis Oost-Limburg

Abstract

Introduction: Intraoperative neuromonitoring (IONM) is considered to increase safety in maximal resection of neurologic tumors. IONM parameter changes have been correlated with postoperative deterioration. Due to the high variability in published data, center-specific warning criteria for IONM parameter changes associated with postoperative neurologic deterioration need to be established. A retrospective study determined the rate, type and severity of postoperative neurologic deterioration in past IONM-assisted neurosurgeries. A prospective observational pilot study examined whether and how IONM parameter changes can be correlated with postoperative neurological deterioration.

Material and methods: In a retrospective chart review of IONM-assisted surgery of (peri-)rolandic brain, cerebellopontine angle (CPA) and spinal lesions, the rate, type and severity of irreversible postoperative deterioration were scored. Next, patient- and lesion-related data were correlated with the occurrence of irreversible postoperative deterioration by univariate logistic regression. In the prospective study, motor cranial nerve (CN), limb muscle strength and/or limb sensory function were assessed 24 hours before, 24-48 hours after and 3 months after IONM-assisted neurosurgery. tMEP, D-wave and SSEP amplitude and latency changes were correlated with limb muscle strength and limb sensory function. Success or failure in mapping of CNs or primary motor cortex and/or corticospinal tract will be correlated with CN function or contralateral limb muscle strength, respectively. Statistical analysis will be performed using linear mixed modeling.

Results: In past IONM-assisted neurosurgeries, 13 of 93 (14%) (peri-)rolandic brain lesion, 20 of 78 (26%) CPA lesion, and 8 of 67 (12%) spine lesion cases had irreversible postoperative deterioration. Re-operation ($p=0.003$), male sex ($p=0.0155$) and schwannomas ($p=0.0329$), and intramedullary location ($p=0.013$) were significantly correlated with deterioration in (peri-)rolandic brain, CPA and spine surgery respectively. In the prospective observational pilot study, no significant correlations were found between IONM parameter changes and postoperative deterioration.

Discussion and conclusions: IONM does not exclude the risk of irreversible postoperative deterioration in (peri-)rolandic brain, CPA and spine surgery. However, postoperative deterioration does not by definition mean complete contralateral hemiparesis, complete facial nerve palsy or complete paraparesis. The lack of significant electrophysiologic-clinical correlations can be due to small sample sizes, heterogenous patient groups and limited variability. However, the postoperative clinical scores show a good outcome in treatment naïve patients without preoperative neurologic deficits. Insights from this study will be used in a large-scale prospective study to obtain sound and reliable electrophysiological-clinical correlations and to establish warning criteria.

1. Introduction

Surgical resection is the first and most effective treatment modality of most mass lesions arising from the nervous system and adjacent structures. To achieve minimal risk of tumor relapse and hence optimal survival, surgical resection of tumors, especially malignant brain tumors (e.g. gliomas), must be as extensive as possible (3, 4). However, if not performed with caution, maximal tumor resection can result in iatrogenic neurologic damage and hence a loss of quality of life (QoL). This is particularly true for resection of (peri-)rolandic brain tumors, cerebellopontine angle (CPA) tumors and spinal cord tumors.

Resection of (peri-)rolandic brain tumors adjacent to eloquent motor cortex and/or the corticospinal tract (CST), holds a risk of contralateral hemiparesis. Similarly, treatment of a (peri-)rolandic brain tumor adjacent to eloquent sensory cortex and/or the thalamocortical tract, can cause a contralateral hemisensory deficit. Removal of CPA tumors can damage adjacent cranial nerves (CNs). The facial nerve (FN) is especially at risk when removing an acoustic neuroma. Due to the proximity of the CST, the medial lemniscus and CNs, resection of brainstem tumors (rare) holds a risk of central nervous deficits as well as CN palsies. In spinal cord tumor surgery, the close confinement of the CST and the dorsal columns to the spinal cord accounts for the substantial risk of para- or tetraparesis and of sensory loss and associated sensory ataxia.

1.1 Onco-functional balance in neurologic tumor resection

To achieve maximal tumor-free survival on the one hand and minimal loss of quality of life on the other hand, surgery must be as extensive as possible without inducing neurologic deficits (or worsening pre-existing deficits) (3, 4). This double aim of tumor resection is reflected in the term "onco-functional balance" (5). Since the presence of mass lesions can result in physical distortion or compensatory reorganization of the nervous system (6), precise information considering individual structural and functional anatomy in relation to the lesion is essential to achieve this onco-functional balance. Furthermore, the appropriate resection plane must be identified to delineate the extent of resection. Therefore, neurosurgeons apply several advanced mapping techniques to visualize, examine and monitor anatomy and function before and during resection (7, 8).

1.2 Preoperative imaging

For patients with lesions located in eloquent brain areas, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) allow pre-surgical, non-invasive, in vivo delineation of the motor cortex and its descending pyramidal tracts (9). fMRI measures change in metabolism and/or cerebral blood flow as a surrogate for neuronal activity using blood oxygenation level-dependent (BOLD) contrast, while the patient performs behavioral tasks (paradigms) (7, 10-12). In contrast to fMRI, which supplies both structural as well as functional information of the eloquent cortex, DTI visualizes subcortical white matter tracts by using MRI to measure the direction of water molecule diffusion as a marker for the axis of these tracts (10, 13, 14). These imaging techniques are performed in favor of surgical planning, risk assessment and selection for invasive mapping techniques (15). Several studies demonstrated that the risk of inducing neurologic deficits depends on the distance between the lesion margin and the eloquent area. For instance, Mueller et al. (16)

reported that no deficits occurred when the distance between resection margin and eloquent cortex was beyond 2 cm, but motor deficits were induced in 33% and 50% of patients with a distance within 1-2 cm and less than 1 cm respectively. Furthermore, Haberg et al. (17) found that the risk of postoperative loss of function was significantly decreased when the lesion-to-eloquent cortex distance was 10 mm or more. Additionally, Krishnan et al. (18) reported that invasive mapping techniques should be performed for a distance to 10 mm, and that a total resection can be achieved safely for distances exceeding 10 mm. For CPA and spine lesions, routine MRI is performed preoperatively to visualize the lesion and its surrounding structures.

1.3 Intraoperative imaging

In addition to preoperative imaging, neurosurgeons use neuronavigation and tumor fluorescence to guide resection. Neuronavigation, used in brain and CPA tumors resection, represents the spatial position of the lesion in real time by integrating presurgical imaging data, which allows co-registration of imaging and patients anatomy (19, 20). Fluorescence-guided surgery applies contrast agent 5-aminolevulinic acid (5-ALA or Gliolan (Medac, Wedel, Germany)) to visualize neoplastic brain tissue (gliomas) using ultraviolet light, as 5-ALA is a natural biochemical precursor of hemoglobin, eliciting synthesis and accumulation of fluorescent porphyrins preferentially in mitotically active tissue (21-23).

1.4 Intraoperative neuromonitoring

Intraoperative neuromonitoring (IONM) permits real-time evaluation of motor and sensory function in anesthetized patients undergoing neurosurgery (24) and is considered to increase safety in maximal tumor resection (25, 26). The basic concept of IONM consists of stimulating a neurologic pathway proximal from the surgical site and recording the accompanying response distant from the surgical site using electrophysiological tests (**Figure 1**), such as somatosensory evoked potentials (SSEP), motor evoked potentials (MEP), and electromyography (EMG) (27). Other IONM modalities, including electroencephalography (EEG), electrocorticography (ECoG), brainstem auditory evoked potentials (BAEP) and visual evoked potentials (VEP) (27), are not routinely applied at our institution and are therefore not discussed in this thesis.

1.4.1 Somatosensory evoked potentials: monitoring of the somatosensory pathways

At Ziekenhuis Oost-Limburg (ZOL), SSEPs are used to monitor the functional integrity of somatosensory pathways in (peri-)rolandic brain and spinal tumor surgery. Other possible applications of SSEPs, such as the phase-reversal technique to localize the central sulcus before proceeding to cortical motor mapping in brain surgery, or dorsal column mapping before proceeding to posterior myelotomy in intramedullary tumor resection (28), are not routinely performed at our institution. The availability of fMRI has supplanted the use of the phase-reversal technique in cortical motor mapping.

SSEPs are evoked by electrical stimulation of the subcutis over the median nerve at the wrist or over the tibial nerve at the ankle, generating an upper limb SSEP (N20) or a lower limb SSEP (P45) at the primary somatosensory cortex (28, 29). SSEP waveforms are defined by an N or P (negative or positive polarity), followed by the nominal poststimulus latency in milliseconds. The standard

responses are based on waveforms recorded in the healthy population (30). The sensory volley contributing to the SSEPs originates at the large peripheral myelinated fibers of the cutaneous and muscle Ia afferents, being the peripheral axons of the first order somatosensory neurons mediating gnostic sensation, consisting of touch, tactile discrimination, position and vibration sense (dorsal column – medial lemniscal pathway). The first order neurons, with their nucleus located in the dorsal root ganglia, project axons to the central nervous system ascending through the ipsilateral dorsal column, up to the cervicomedullary junction. At this level, the axons originating from the lower and upper limbs synapse with second order somatosensory neurons at the nucleus gracilis (medial) and the nucleus cuneatus (lateral) respectively. The second order neurons' axons form the medial lemniscus, cross the midline and project to the ventral posterolateral nucleus (VPL) of the contralateral thalamus, where they synapse with the third order somatosensory neurons. Finally, the third order neurons' axons project to the parietal sensory cortex. Note that the small fiber sensory system, mediating pain and temperature sensation, does not contribute to SSEPs, due to the smaller diameter of these fibers, which are not sufficiently stimulated at the intensities employed in clinical practice (**Figure 2a**) (28).

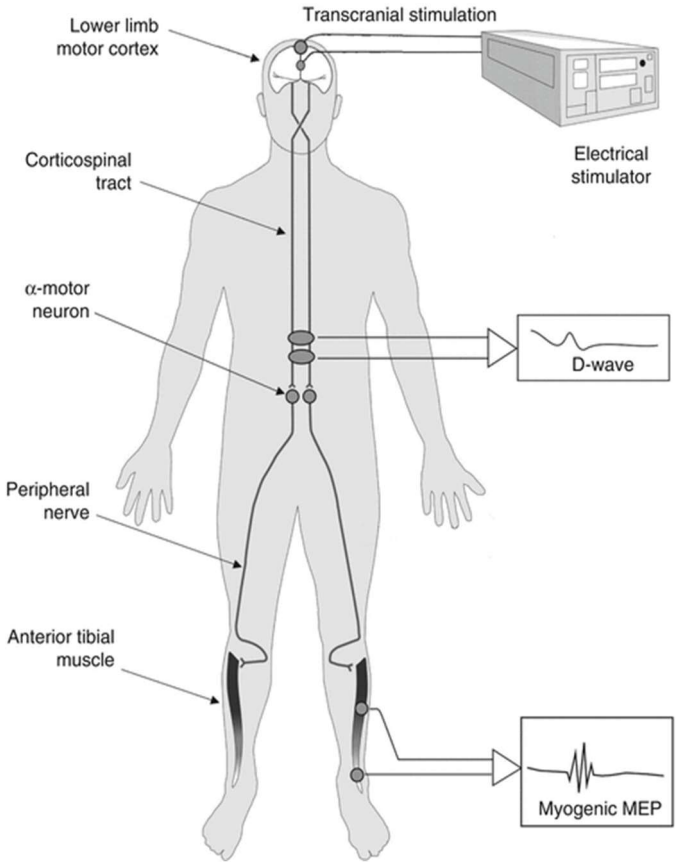

Figure 1: Schematic representation of transcranial motor evoked potential (tMEP) stimulation and recording. The basic concept of transcranial motor evoked potentials consists of stimulating the corticospinal tract at its origin (motor cortex) and recording the accompanying response distally, either at the spinal cord (D-wave) or at the limb muscles (myogenic MEP). *(Adapted from Schwartz DM, Sestokas AK, Franco AJ, Dormans JP. Intraoperative Neurophysiological Monitoring During Corrective Spine Surgery in the Growing Child. In: Akbarnia BA, Yazici M, Thompson GH, editors. The Growing Spine: Management of Spinal Disorders in Young Children. Berlin, Heidelberg: Springer Berlin Heidelberg; 2016. p. 883-95. (1))*

1.4.2 Motor evoked potentials: monitoring and mapping of motor pathways

Transcranial muscle MEPs (tMEPs) and direct (D-)waves are utilized for continuous monitoring of the functional integrity of the motor pathways. Indications of tMEPs parallel those of SSEP monitoring (rolandic brain and spine lesions) (28). The use of D-waves is limited to cervical and (upper) thoracic spine surgery, but D-wave deterioration is considered more specific to postoperative motor deficits than tMEPs deterioration (25). Direct MEPs (dMEPs) allow identification of primary motor cortex (PMC) (direct cortical stimulation, DCS) and assessment of proximity of the CST (direct subcortical stimulation, DSCS), which is based on the near-linear correlation between stimulation intensity (mA) and distance to the CST (mm) (31). Consequently, dMEPs are exclusively applied in rolandic brain tumor surgery.

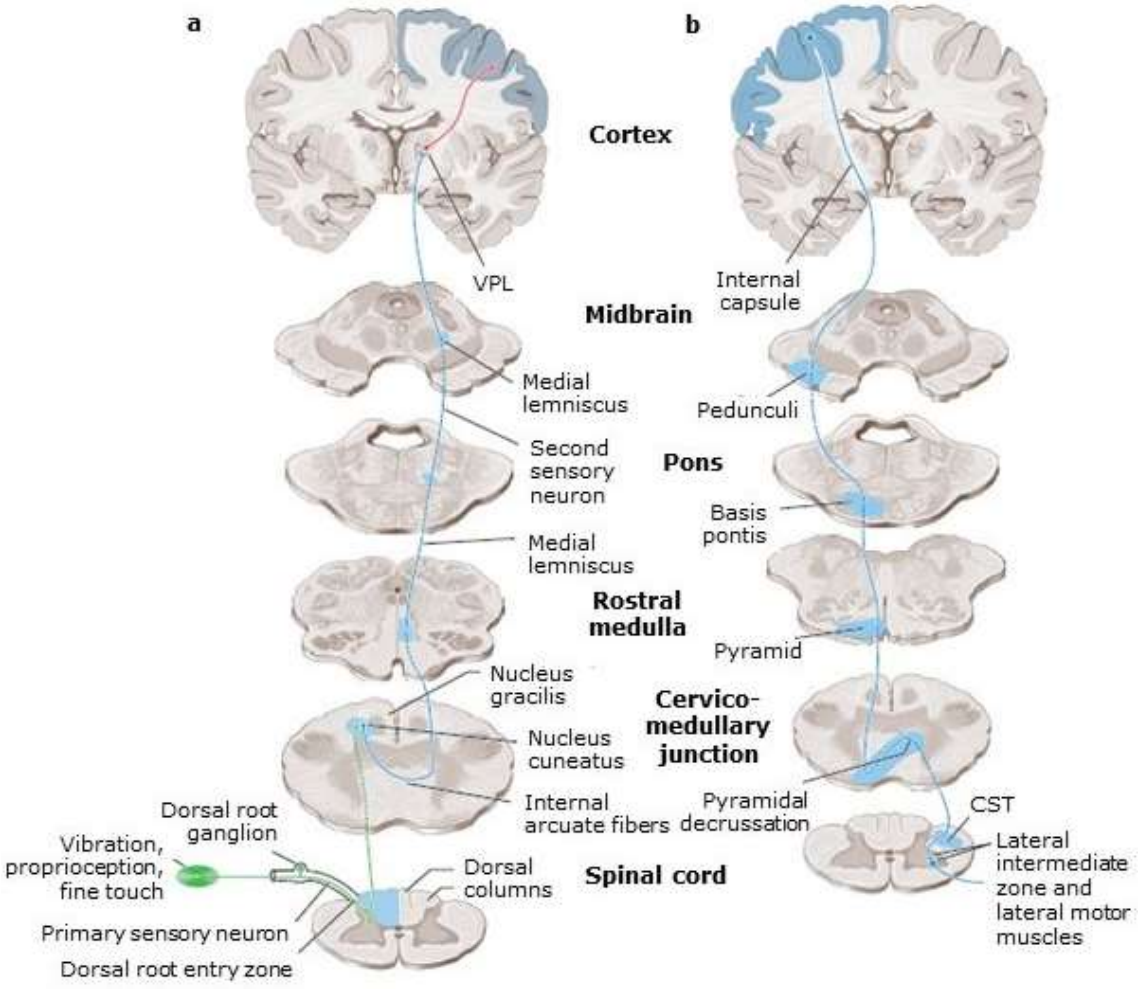

Figure 2: The major sensory and motor pathways contributing to somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs). a: The dorsal column – medial lemniscal pathway contributes to SSEPs and mediates gnostic sensation. The sensory volley entering the spinal cord via the first order sensory fibers ascends through the ipsilateral dorsal column to the cervicomedullary junction. At this level, the axons synapse with the second order neurons at the nucleus gracilis and nucleus cuneatus. These neurons form the medial lemniscus, cross the midline, and project to the ventral posterolateral nucleus of the contralateral thalamus, where they synapse with the third order neurons, in turn projecting to the sensory cortex. **b:** The lateral CST contributes to MEPs and conducts the motor volley, arising in the upper motor neurons of the primary motor cortex. After descending through the corona radiata and diverging at the internal capsule they form the cerebral crura at midbrain level and form the medullary pyramids below. The fibers cross at the cervicomedullary junction, travel through the contralateral lateral funiculus, to end in the cervical and lumbar spinal cord, where they synapse directly or indirectly on lower motor neurons, innervating their respective myotomes via peripheral motor nerves. CST: corticospinal tract, VPL: ventral posterolateral nucleus. *(Adapted from Blumenfeld H. Neuroanatomy through clinical cases. 2nd ed. Sunderland: Sinauer Associates; 2010. 1006 p. (2))*

MEPs are evoked by applying an electrical current to the PMC, either transcranially (tMEP) or directly on the tissue (dMEP). dMEPs can be generated by stimulating the PMC (DCS) and/or the subcortical white matter adjacent to the CST (DSCS). tMEPs and dMEPs are recorded at the contralateral limb muscles (muscle MEP, mMEP), whereas D-waves are recorded at the spinal cord (**Figure 1**) tMEPs are preferentially recorded in distal limb muscles, as their important cortical representation tends to result in more successful stimulation than proximal limb muscles with a limited cortical representation (28, 32). The transcranially elicited electrical volley starts at the corticospinal axons, arising in the upper motor neurons of the PMC and descending through the corona radiata. After converging at the internal capsule (diencephalic level), they form the cerebral crura at midbrain level. Below, the fibers form the medullary pyramids and split at the cervicomedullary junction, with most of them crossing and travelling through the lateral funiculus, contralateral to the hemisphere of origin. The lateral CST (simply referred to as CST) ends in the cervical (upper limb muscles) and lumbar (lower limb muscles) spinal cord. Finally, the CST axons synapse directly or indirectly on lower motor neurons, whose axons exit the spinal cord through the ventral roots and innervate their respective myotomes via peripheral motor nerves (**Figure 2b**) (28).

1.4.3 Electromyography: monitoring and mapping of motor nerves

EMG enables monitoring and mapping of the motor component of the peripheral nervous system, to preserve the integrity of CNs, nerve roots and peripheral nerves (28, 33). At our department, EMG is most commonly used to map motor (components of) cranial nerves in CPA tumor surgery, especially the facial nerve (n. VII), innervating the muscles of facial expression. Other cranial nerves eligible for monitoring include the oculomotor (n. III), the trochlear (n. IV) and the abducens (n. VI) nerves, innervating the extra-ocular muscles; the trigeminal nerve (n. V), innervating the jaw muscles; the glossopharyngeal (n. IX) and the vagus (n. X) nerves, innervating pharyngeal and laryngeal muscles; the accessory nerve (n. XI), innervating the trapezius and sternocleidomastoid muscles, and the hypoglossal nerve (n. XII), innervating the tongue muscles.

The basic EMG techniques include free-run EMG and triggered EMG. Free-run EMG is used as a continuous monitoring tool to detect surgically driven mechanical and/or metabolic irritation of the nerve by recording spontaneous muscle activity, which is represented by spontaneous muscle motor unit potentials (27, 28). Two types of discharge, each with different clinical significance, can be distinguished: tonic discharge and phasic discharge. Tonic discharge consists of repetitive and steady episodes of electrical responses, lasting several seconds to minutes. It may occur in nerve ischemia due to traction on the nerve, thermal stimulation from electrocautery, or irrigation with saline (27). On the other hand, phasic discharge is a short and relatively synchronous burst of motor unit potentials, lasting no longer than a second (27). It is mostly associated with blunt mechanical damage (27, 33). Triggered EMG is performed by electrical stimulation of cranial or peripheral motor nerves or roots with a hand-held sterile device, evoking compound muscle action potentials (CMAPs) in the corresponding muscles (27, 28, 33). It is used as a mapping tool to localize and identify cranial or peripheral nerves that are often difficult to distinguish from each other as well as from tumoral, fibrous and fatty tissue (28), and to evaluate its proximity to the surgical area (27).

1.4.4 Correlation of IONM parameter changes and neurologic outcome

In continuous SSEP and MEP monitoring, amplitude and latency changes have been correlated with iatrogenic damage to the sensory and motor pathways respectively. Reproducible SSEP and MEP parameter changes are reported to the surgeon, who then decides whether to adapt the course of the surgical procedure to reduce the risk of permanent damage. Likewise, in cortical, subcortical and motor (cranial) nerve mapping, the proximity of eloquent nervous structures warrants caution in further tumor resection.

1.5 Factors influencing IONM responses

However, IONM parameter changes should be carefully interpreted, since several factors can cause false positive IONM parameter changes as well as false negative failure of mapping. These factors include anesthesia, systemic factors, or technically induced and surgery-related artefacts.

1.5.1 Anesthesia

SSEP and MEP latency and amplitude can significantly be affected by the type and depth of anesthesia (27). The choice of anesthetic agents is therefore determined by 1) the interaction of the anesthetic agents with the patient's pathophysiology, 2) surgical requirements, and 3) the specific IONM modalities to be used. Most anesthetics tend to decrease neural conduction and synaptic transmission, and thus decrease the amplitude and increase the latency of IONM potentials. This effect appears to be dose-related, although many agents have disproportionate effects at low clinical dosages (34).

Halogenated inhalation agents profoundly decrease the amplitude and increase the latency of both SSEPs (29) and transcranial MEPs (35), and can even abolish tMEP recordings at low concentrations (e.g. <0.2-0.5 MAC) (36). The effect of halogenated inhalation agents on IONM increases with higher mean alveolar concentration (MAC) (35). DSC can overcome halogenated inhalation agent-induced mMEP decrease. Myogenic responses can be observed at 0.75 to 1.5 MAC isoflurane and sevoflurane following DCS (37). D-waves are resistant to inhalational agents, as this response does not require synaptic transmission. However, high concentrations of inhalation agents can mildly reduce D-wave amplitude (38, 39). Nitrous oxide (N_2O) causes amplitude reduction and latency increase in SSEPs and tMEPs as well. Compared to other inhalation agents at equipotent anesthetic concentrations, N_2O produces the most profound SSEP and tMEP parameter changes. The effects of N_2O on D-waves are minimal (34) and better success rates have been demonstrated under combinations of halogenated agents and N_2O after DCS (37).

Total intravenous anesthesia (TIVA) is the preferred choice for monitoring purposes. Propofol as sedative agent and an opioid as analgesic are widely recommended, as these agents enable consistent successful MEP and SSEP monitoring (29, 32). Propofol induction only slightly decreases amplitude and increases latency of MEPs and SSEPs (34). This effect is readily reversible after termination of infusion, due to the rapid metabolism and titratability of propofol (40). The effects of opioid analgesics on EPs are also generally mild (34, 35). The deterioration of EP amplitude and latency due to propofol and opioids are substantially less than with equipotent doses of halogenated inhalation anesthetics (34, 41) and appears to be related to drug concentrations, since maximal deterioration occurs when drug concentrations peak, typically after bolus drug delivery (34).

Other intravenous agents favorable for IONM include ketamine, etomidate and benzodiazepines. Ketamine tends to increase the amplitude of EPs (42, 43). Although ketamine provides excellent analgesia and hypnosis, side effects including postoperative hallucinations, increased intracranial pressure, and adverse cardiac effects make its use undesirable (42). Furthermore, its long half-life may confound postoperative neurologic examination (38, 42). The occurrence of postoperative hallucinations can be minimized by pre- and intraoperative administration of a benzodiazepine (34, 42), which causes only mild depression of EPs (44). EP recordings unsuitable for monitoring purposes can be enhanced by constant infusion of etomidate as well (45).

The use of muscle relaxants during surgery affects signal transmission across the neuromuscular junction, resulting in amplitude depression or even abolishment of MEPs and EMG (33, 34, 46), especially in patients with pre-existing motor deficits (47). However, partial and controlled neuromuscular blockage can reduce body movements that follow transcranial stimulation, thus improving patient safety and neutralizing interference with the surgeon's microscopic view. Despite these benefits, most neurophysiologists avoid the use of muscle relaxants for tMEP and EMG monitoring. Their use is limited to facilitate endotracheal intubation (33, 34, 46). Neuromuscular blockage does not affect D-waves (48) and can even improve the quality of SSEPs by reducing electromyographic interference from muscle groups near the SSEP recording electrodes (29, 34).

1.5.2 Systemic factors

Systemic factors may cause IONM parameter changes, unrelated to neurologic damage. SSEP and MEP amplitudes decrease and latencies increase when blood pressure drops and the metabolic demands of neural tissue are not met, due to insufficient neural perfusion. SSEPs deteriorate when cortical blood flow falls beneath 18 ml/100 g/min. A drop of cortical blood flow beneath 15 ml/100 g/min results in a loss of SEPPs. In general, deterioration appears to be minimal when systolic blood pressure is kept stable at 80 mm Hg (29). MEP deterioration in baboons was induced by cortical ischemia when cortical blood flow dropped below 16 ml/100 g/min (49).

Hypothermia and local cooling, for instance by cold irrigation, diminish nerve conduction velocity, resulting in SSEP and MEP latency prolongation (29, 32). Furthermore, the stimulation threshold increases with decreasing temperature, reflecting reduced motor cortical excitability. In mild hypothermia (body temperature 31 to 34°C), reproducible mMEPs can be obtained, although latencies lengthen when body temperature drops below 32°C (50). Loss of D-waves occurs at 25°C in patients under circulatory arrest (50) but reverses after rewarming to normothermia (51). SSEPs disappear at approximately 22°C (52).

Other systemic factors, such as scalp edema, severe electrolyte disturbances, hypoxemia, hypercapnia, hypocapnia or anemia can result in MEP deterioration (32).

1.5.3 Artefacts

Various IONM parameter changes result from technical artefacts, such as malfunction of the IONM device, displacement and/or high impedance of the electrodes and inappropriate settings. Furthermore, artefacts in IONM signals are commonly observed to be surgery-related, for example electrocautery, hammering, surgical manipulation, and traction or compression on neural tissue.

Therefore, the role of an experienced neurophysiologist is crucial in discriminating these artefacts from IONM changes related to neural damage (27).

1.6 The scarcity of evidence and variability in IONM warning criteria

Despite the increasing use of IONM in several neurosurgical procedures, the limited number of randomized controlled trials is a major limitation in proving better neurologic outcome in IONM-assisted compared to non-IONM-assisted surgery (24, 53). The various electrophysiological techniques and their use in anesthetized neurosurgical patients have gradually been developed for more than a century (29, 32, 54) and thus were incorporated in clinical practice before the era of controlled studies. Additionally, conducting randomized controlled trials implies serious ethical dilemmas. Since IONM is considered standard of care in a growing number of neurosurgical centers, not offering patients suffering from aggressive neurologic tumors the best available treatment does not seem acceptable (24, 53). Nevertheless, there is a considerable amount of lower level evidence indirectly supporting the efficacy of IONM, as several authors have reported correlations between IONM parameter changes, such as latency increase or amplitude decrease of SSEPs, MEPs, D-waves and CMAPs (triggered EMG) on the one hand, and postoperative neurologic deterioration in various surgical procedures, including IMSCT surgery (55), peri-rolandic brain surgery (48), and facial nerve monitoring (56), on the other hand. However, there is an ongoing debate on whether IONM requires controlled studies (24) or whether expert consensus suffices (57).

Secondly, the high intra- and interpatient trial-to-trial amplitude variability of tMEPs, probably caused by the variable activation of higher (brain) and lower (spinal cord) motor neurons, confounds the interpretation of tMEP parameter changes. This variability impedes the determination of a clear cut-off value, in terms of amplitude change, as warning criterium for an impending motor deficit (58). However, several attempts to establish such warning criteria have been suggested, including the loss of response (25), several degrees of amplitude decrease and/or latency increase (48), and finally an increase in stimulation threshold (59). The high rate of variability in these warning criteria can be due to differences in anesthesia protocols as well as in monitoring techniques and devices in different centers. As a result, no standardized IONM protocols nor universally valid warning criteria are established at present (32). Therefore, it is desirable to establish center-specific warning criteria for IONM signal change associated with neurologic deterioration.

1.7 Objectives

First, a retrospective study determined the rate of postoperative neurologic deterioration despite IONM-assistance in past neurosurgeries. The risk of irreversible neurologic deterioration was then correlated with patient- and lesion-related features. Second, a prospective observational pilot study examined whether and how IONM parameter changes and postoperative neurologic deterioration could be correlated and whether center-specific warning criteria could be established. The results and insights of this pilot study will be used in future studies with the aim to further reduce the risk of irreversible neurologic deterioration in (peri-)rolandic brain, CPA and spinal cord tumor surgery at ZOL, by optimal use of multimodal IONM.

2. Material and methods

2.1 Retrospective study

2.1.1 Patients and exclusion criteria

Between January 1st, 2011 and October 31st, 2017, a total of 259 patients suffering from (peri-)rolandic brain, CPA, spine and other neurologic (PN and fourth ventricle) lesions were treated with IONM-assisted surgery at the Neurosurgical department of Ziekenhuis Oost-Limburg, Genk, Belgium. Pre- and postoperative clinical and radiological reports of the included patients have been retrospectively reviewed. Patient were excluded from the study if 1) IONM failed; 2) serious postoperative adverse events influenced neurologic outcome; 3) data were incomplete due to death or lost to follow up. All other patients were included in the study, regardless of neurologic condition at time of presentation or prior treatment history.

Thirteen patients were excluded from the study. MEPs could not be elicited in 10 patients. Failure of obtaining MEPs was due to preoperative severe paresis or paralysis in 6 patients (1 brain, 1 CPA and 4 spine lesion), to technical defects in 1 patient (brain lesion), to an underdeveloped nervous system in 1 neonate (spine lesion), to administration of muscle relaxants in 1 patient (CPA lesion) and to electrode disconnection during positioning in 1 patient (spine lesion). Postoperative bleeding influenced neurologic outcome in 1 CPA lesion patient and 1 spine lesion patient. One CPA lesion patient died before a postoperative neurologic examination could be performed. No patients were lost to follow up.

2.1.2 Outcome, patient and lesion data collection

Preoperative, short-term (24 to 48 hours) postoperative and long-term (three months) postoperative clinical status of every included patient was recorded. Severity of motor deficit of an entire limb was scored according to the simplified Medical Research Council (MRC) scale for limb muscle strength (0: complete paralysis, 1: severe weakness, 2: slight weakness, 3: normal strength) (**Table 1**) in patients with (peri-)rolandic brain lesions, 4th ventricle lesions and spine lesions. The clinical reports did not allow detailed scoring of every separate limb muscle. Severity of sensory deficit of an entire limb and CN motor deficit were scored according to an analogous severity scale (0: complete deficit, 1: severe deficit, 2: slight deficit, 3: normal). Sensory deficit was scored in patients with (peri-)rolandic brain lesions, 4th ventricle lesions and spine lesions. CN and PN motor deficit was scored in patients with CPA and PN lesions. Irreversible postoperative neurologic deterioration was quantified by comparing preoperative and long-term (three months) postoperative scores.

Table 1: Simplified Medical Research Council (MRC) scale.

Grade	Muscle strength
0	Complete paralysis
1	Severe weakness (> 50% loss)
2	Slight weakness (< 50% loss)
3	Normal strength

Patient characteristics (age, gender, presence of pre-existing deficit) and lesion characteristics (location, histology, recurrence) were recorded and correlated with irreversible postoperative neurologic deterioration after IONM-assisted surgery in patients with (peri)-rolandic brain, CPA and spine lesions separately. Patients with (peri-)rolandic brain and CPA lesions were divided in three age categories: 16 to 35 years, 36 to 55 years and 56 to 85 years. Patients with spine lesions were divided in two age categories: 16 to 55 years and 56 to 85 years. MRI scans and radiological reports were reviewed to determine the lesion location. Laterality (left or right side) was recorded in brain and CPA lesions. In brain lesions, fMRI scans and corresponding radiological reports were reviewed to determine the lesion-to-eloquence distance (distance between the lesion and the PMC and/or CST). A lesion-to-eloquence distance of 10 mm or less was defined as a high-risk location. In spine lesions, the spinal level (cervical, thoracic or lumbosacral) as well as the intramedullary or extramedullary (further subdivided in intradural and extradural) location was recorded. Tethered cord syndrome was excluded from the correlation analysis between location and irreversible postoperative deterioration, since no irreversible deficits were observed in these cases. Definite histological diagnosis was obtained from pathology reports. Brain lesions were stratified in glioma, metastasis and other lesions. CPA lesions were divided into schwannoma, meningioma and other lesions. Spine lesions included ependymomas and other lesions. Repeat surgery to treat lesion recurrence was defined as a reoperation. Data of patients with PN and fourth ventricle lesions were used for descriptive objectives only and excluded from further analysis, because of the small sample size and the absence of irreversible postoperative neurologic deterioration in PN lesion patients.

2.1.3 Statistical analysis

Within every separate group (brain, CPA and spine), the patient- and lesion-related variables were correlated with irreversible postoperative deterioration by univariate logistic regression. A prediction model for irreversible postoperative deterioration was built using forward modeling, consisting of statistically significant patient and lesion variables. This model was compared with an intuition model, consisting of patient and lesion variables considered predictive for irreversible deterioration by the neurosurgeons most experienced in IONM-assisted surgery at our institution. The model with the lowest Bayesian information criterion (BIC) value was considered the best model. The threshold of statistical significance was set at $P<0.05$.

2.2 Prospective observational pilot study

2.2.1 Patients and exclusion criteria

The present study was approved by the Committee for Medical Ethics of ZOL, Genk, Belgium. A total of 35 consecutive patients with (peri-)rolandic brain, CPA, spine and PN lesions were treated with IONM-assisted surgery at the Neurosurgical department of Ziekenhuis Oost-Limburg, Genk, Belgium between November 1st, 2017 and May 2nd, 2018. The neurosurgeons determined the indication for IONM-assistance, based on size, location, and type of the lesion. The single patient with a PN lesion was excluded from the study (small sample size). Other exclusion criteria were IONM failure (see results section) and serious adverse events confounding the postoperative neurological examination (2 patients). One CPA lesion patient suffered from postoperative cerebellar edema and was treated

by urgent fossa posterior decompression. One brain lesion patient was excluded because of a peri- or postoperative stroke.

2.2.2 Clinical neurological examination

Study patients had a neurological examination within 24 hours before and 24 to 48 hours after neurosurgery. In case of postoperative deterioration, the clinical examination was repeated three months after surgery. The emphasis of the clinical examination in patients with (peri-)rolandic brain lesion was on muscle strength in contralateral upper (deltoid, biceps, triceps, wrist flexors, wrist extensors and hand muscles) and lower (iliopsoas, quadriceps, hamstrings, ankle flexors and ankle extensors) limbs. If the brain lesion extended towards the primary sensory cortex and/or the thalamocortical tract, sensation in contralateral upper and lower limbs was examined. Patients with spinal lesions were examined for muscle strength and sensation (cervical lesions: bilateral upper and lower limbs; thoracic and lumbosacral lesions: bilateral lower limbs). In patients with CPA lesions, muscle function of the relevant CNs (the CN at risk being dependent on the exact location of the lesion) was examined. Limb muscle strength was scored according to a modified MRC scale (**Table 2**). In order to calculate differences in preoperative, short-term and long-term postoperative MRC scores, these scores were adapted as demonstrated in **Table 2**. Sensation and CN paresis was scored according to the scoring systems applied in the retrospective study (0: complete deficit, 1: severe deficit, 2: slight deficit, 3: normal function). Postoperative neurologic deterioration was quantified by comparing preoperative and short term (24 to 48 hours) postoperative scores. Repeat clinical examination after three months was performed to assess the reversible or irreversible nature of postoperative deficits.

Table 2: Modified Medical Research Council (MRC) scale.

Grade	Adapted score	Muscle strength	Grade	Adapted score	Muscle strenght
0	0	Complete paralysis	**3+**	6	Brief active movement against slight resistance*
1	1	Minimal contraction	**4-**	7	Sustained active movement against slight resistance*
2	2	Active movement with gravity eliminated	**4**	8	Active movement against slight resistance**
2+	3	Brief active movement against gravity*	**4+**	9	Movement against strong resistance*
3-	4	Sustained active movement against gravity*	**5-**	10	Movement against strong resistance**
3	5	Active movement against gravity**	**5**	11	Normal strength

*<50%, **>50% range of joint movement

2.2.3 Intraoperative SSEP monitoring

SSEPs were elicited by rectangular positive single pulse stimulation of the posterior tibial nerve at the ankle (lower limb SSEPs) and of the median nerve at the wrist (upper limb SSEPs) using disposable red/black stainless steel subdermal needle electrodes (Inomed Medizintechnik GmbH, Emmendingen, Germany). Stimulus intensity was set at 10% above the motor threshold (mostly 15 to 25 mA) with a stimulus duration of 200 µs and a repetition rate of 4.7 Hz (upper limb) and 3.7 Hz (lower limb). SSEPs were recorded at the scalp overlying the contralateral primary sensory cortex using disposable green stainless steel subdermal needle electrodes (Inomed Medizintechnik GmbH, Emmendingen, Germany). A similar ground electrode was placed above the trapezius muscle. The following subdermal needle electrode derivations were used: CP3-Fz (right upper limb), CP4-Fz (left upper limb) and CPz-Fz (lower limbs), with electrode denomination referring to the 10-20 International EEG electrode system (**Figure 4**). Signals were amplified with a filter bandpass between 0.5 Hz and 200 Hz and averaged at 100 (upper limb) and 150 (lower limb) stimulations. SSEPs were quantified by latency and amplitude (**Figure 3**). Upper limb SSEP (N20) latency was measured from the start of stimulation to the onset of the negative (upward) slope (milliseconds). N20 amplitude was measured from peak to trough (microvolts). Lower limb SSEP (P45) latency was measured from the start of stimulation to the onset of the positive (downward) slope (milliseconds). P45 amplitude was measured from trough to peak (microvolts). Baseline measurements were performed immediately prior to onset of tumor resection.

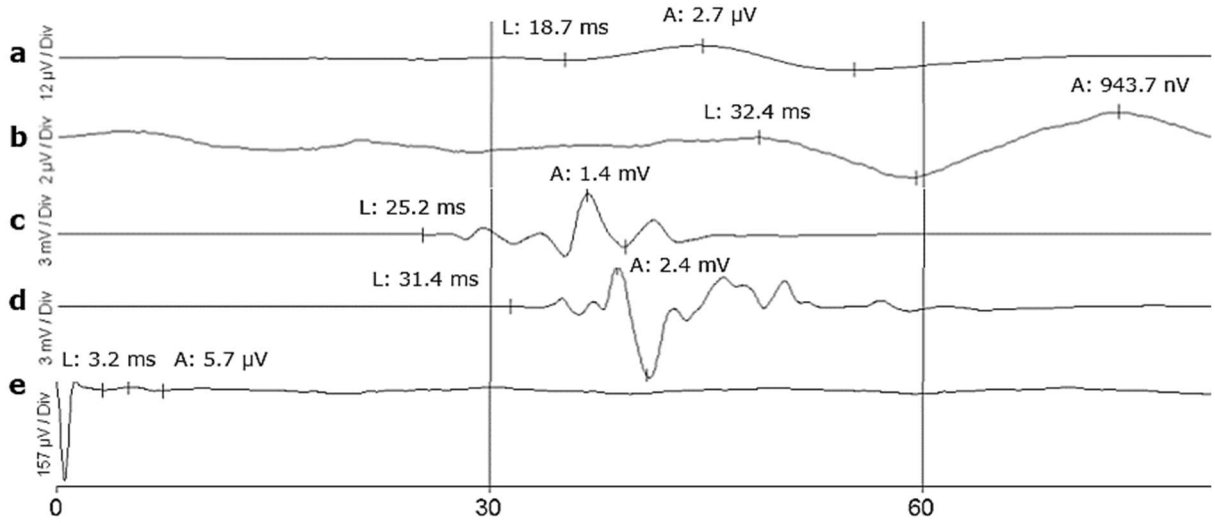

Figure 3: Measurement of latency (L) and amplitude (A). a: Upper limb SSEP (N20) amplitude (microvolts) and latency (milliseconds); **b:** Lower limb SSEP (P45) amplitude (nanovolts) and latency (milliseconds); **c:** Upper limb MEP (m. abductor policis brevis) amplitude (millivolts) and latency (milliseconds); **d:** Lower limb MEP (m. tibialis anterior) amplitude (millivolts) and latency (milliseconds); **e:** D-wave amplitude (microvolts) and latency (milliseconds).

2.2.4 Intraoperative MEP and D-wave monitoring

tMEPs were elicited by transcranial electrical stimulation of the scalp on position C3-C4 (10-20 International EEG electrode system, **Figure 4**) using disposable red/black stainless steel subdermal needle electrodes. Electrical stimulation was performed using rectangular positive (right limb) or negative (left limb) train-of-five stimuli of 500 µs duration with an interstimulus interval (ISI) of 5 ms, a repetition rate of 1 Hz and intensities between 80 mA and 200 mA. A disposable green stainless steel subdermal needle ground electrode was placed above the vastus lateralis muscle. In patients

with (peri-)rolandic brain lesions, tMEPs were recorded at the contralateral upper limb (m. brachioradialis and m. abductor policis brevis) and lower limb (m. tibialis anterior and m. extensor digitorum communis brevis muscle). In spinal lesion patients, muscle sampling was dependent on the spinal level. In cervical lesions, tMEPs were recorded in the four limbs (left and right m. brachioradialis, m. abductor policis brevis, m. tibialis anterior and m. extensor digitorum communis brevis). In thoracic and lumbosacral lesion, tMEPs were recorded in both lower limbs (m. vastus lateralis, m. tibialis anterior and m. extensor digitorum communis brevis). In one case of thoracic meningioma, tMEPs were recorded from three distal lower limb muscles (m. tibialis anterior, m. gastrocnemius and m. extensor digitorum communis brevis), to enhance the probability to obtain MEPs in the paretic lower limbs. In one case of lumbosacral root schwannoma, MEPs were recorded at index muscles of the myotomes L4 (m. vastus lateralis), L5 (m. tibialis anterior) and S1 (m. gastrocnemius), a setting imposed by the need for nerve root mapping with triggered EMG. Disposable red/black recording electrodes were placed intramuscular in all cases. A disposable green stainless steel subdermal needle ground electrode was placed above the vastus lateralis muscle. Signals were amplified with a filter bandpass between 0.5 Hz and 2000 Hz. MEPs were quantified by latency and amplitude (**Figure 3**). MEP latency was measured from the start of the train pulse stimulation to the onset of the MEP signal. As MEPs typically have a polyphasic morphology, amplitude was measured from peak to trough in the phase with maximal positive peak. Baseline measurement was performed immediately prior to onset of tumor resection.

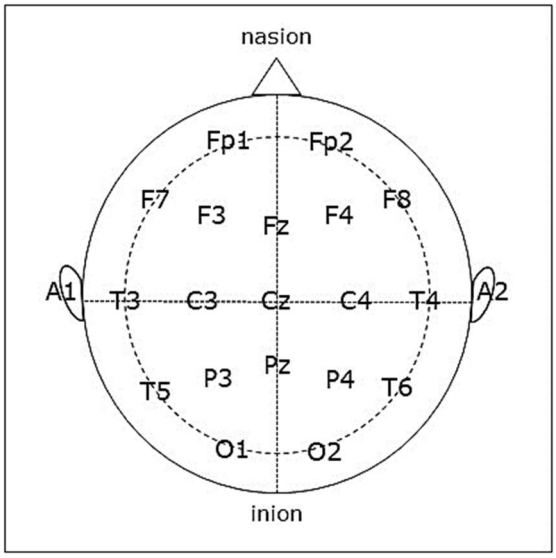

Figure 4: The international 10-20 system for electrode placement on the scalp. Fp, pre-frontal; F, frontal; C, central; T, temporal; P, parietal; O, occipital; A, mastoid process; a 'z' (zero) refers to a electrode placed on the midline sagittal plane of the skull and is mostly used as reference point.

D-waves were evoked by biphasic single pulse stimulation of 1250 ms through the same electrodes as used for evoking tMEPs. A disposable flexible two-pole electrode (Inomed Medizintechnik GmbH, Emmendingen, Germany) was placed in the subdural space following opening of the dura mater. Recordings were averaged at three stimulations. D-waves were quantified by latency and amplitude (**Figure 3**). D-wave latency was measured from the start of stimulation to the onset of the upward

slope. Amplitude was measured from peak to trough. Baseline measurement was performed immediately prior to onset of tumor resection.

2.2.5 Cortical and subcortical motor mapping

In (peri-)rolandic brain lesion patients, dMEPs were generated by stimulation of the PMC and/or subcortical white matter adjacent to the CST using a disposable ball tip bayonet shaped monopolar probe (Inomed Medizintechnik GmbH, Emmendingen, Germany) with a neutral subdermal reference needle electrode placed in the surrounding tissue. Cortical stimulation consisted of positive train-of-three stimuli of 10 to 30 mA, 300 µs duration, 4 ms ISI and 1 Hz repetition rate. Subcortical stimulation consisted of negative train-of-three stimuli of 0.9 to 20 mA, 600 µs duration, 4 ms ISI and 1 Hz repetition rate. Recording occurred through the same electrodes as those recording tMEPs. In DCS and DSCS, success of mapping was recorded with indication of the accompanying recorded muscle. In DSCS, the motor threshold was recorded as well, indicating the proximity of the CST.

2.2.6 Cranial nerve mapping

In CPA lesion patients, the facial nerve and other motor (components of) CNs were triggered by negative single pulse stimuli with an intensity of 0.1 to 1 mA, duration of 200 µs and repetition rate of 3 Hz using a disposable bayonet shaped concentric bipolar probe (Inomed Medizintechnik GmbH, Emmendingen, Germany). CMAPs were recorded at the muscle(s) innervated by the CN of interest (**Table 3**), using red/black subdermal electrodes. Recordings from the vagus nerve were obtained from a NIM FLEX™ EMG endotracheal tube (Medtronic Xomed Inc, Jacksonville, FL, USA) inserted at intubation.

Table 3: Placement of recording electrodes in cranial nerve mapping

No.	Cranial nerve	Recorded muscle
n. III	n. oculomotorius	m. rectus superior
n. IV	n. trochlearis	m. obliquus superior
n. V	n. trigeminus	m. masseter m. temporalis
n. VI	n. abducens	m. rectus lateralis
n. VII	n. facialis	m. orbicularis oculi m. orbicularis oris
n. IX	n. glossopharyngeus	m. glossopharyngeus
n. X	n. vagus	m. vocalis
n. XI	n. accessorius	m. sternocleidomastoideus m. trapezius
n. XII	n. hypoglossus	m. hypoglossus

2.2.7 Statistical analysis

In patients with (peri-)rolandic brain lesions and spine lesions, IONM parameter changes were correlated with changes in neurologic status using univariate (linear) mixed models. Univariate regression is used when data did not consist of repeated measurements (D-waves). When sample

sizes are rather small, nonparametric alternatives (Spearman correlation) are used instead. The threshold of statistical significance was set at $P<0.05$ for all analyses. In (peri-)rolandic brain lesion patients, tMEP amplitude and latency changes were correlated with differences between pre- and postoperative MRC score in the corresponding distal limb muscle. The average and the median tMEP amplitude and latency, as well as the single best tMEP amplitude and latency, of the first 5 minutes after onset of tumor resection and the last 5 minutes of tumor resection were calcultated. tMEP amplitude change was defined as $(Amp_{start}–Amp_{end})/Amp_{start}$ (analogous for latency change). To investigate whether amplitude and latency change of tMEPs recorded in a distal limb muscle can predict proximal limb muscle paresis, the correlation of tMEP amplitude and latency, calculated by the 3 methods described earlier, was made with a non-monitored, but clinically scored (MRC scale) proximal limb muscle (**Table 4**). Success or failure of cortical and subcortical mapping and motor thresholds in subcortical mapping were each correlated with differences in MRC scores. Correlation analysis of SEPP amplitude and latency with contralateral sensation was not performed, due to the small sample size ($n = 1$). In CPA lesion patients, success or failure of CN mapping (triggered EMG) was correlated with differences in postoperative CN palsy. In spine lesion patients, SSEP, tMEP and D-wave amplitude and latency changes were correlated with differences in clinical scores. tMEP amplitude and latency changes were correlated with differences in MRC score in the corresponding distal limb muscle. To investigate whether amplitude and latency change of tMEPs recorded in a distal muscle can predict proximal muscle paresis, the correlation of tMEP amplitude and latency, was made with a non-monitored, but clinically scored (MRC scale) proximal limb muscle (**Table 4**). Correlation analysis of SEPP amplitude and latency changes with differences in limb sensation was performed for lower limbs. Upper limb SSEPs were performed in only one patient. D-wave amplitude and latency changes were correlated with the differences in average MRC score of both ankle extensor muscles.

Table 4: Corresponding recorded and clinical scored distal and proximal limb muscles.

Recorded muscle	Scored distal muscle	Scored proximal muscle
Brachioradialis	Biceps	-
Abductor policis brevis	Hand	Deltoid
Tibialis anterior	Ankle extensors	Iliopsoas
Extensor digitorum communis brevis	Ankle extensors	-
Gastrocnemius	Ankle flexors	-
Vastus lateralis	Quadriceps	-

3. Results

3.1 Retrospective study

The retrospective study analyzed the neurologic outcome in past IONM-assisted neurosurgeries. First, patient- and lesion-related data are presented. Second, the proportion, type and severity of irreversible postoperative neurologic deterioration despite IONM-assistance is described. Third, patient- and lesion-related characteristics were correlated with irreversible deterioration. Finally, a prediction model, based on the characteristics significantly correlating with irreversible deterioration, was compared with an intuition model, based on the expert opinion of the neurosurgeons acquainted with IONM-assisted surgery.

3.1.1 Patient and lesion characteristics

A total of 246 patients, 117 (47.6%) men and 129 (52.6%) women, were included in the retrospective study. Their mean age was 53.7 ± 14.2 years. These patients were divided into four groups according to the location of their lesions in the nervous system.

Among the 93 (peri-)rolandic brain lesion patients (mean age 53.5 ± 14.9 years), consisting of 51 men (54.8%) and 42 women (45.2%), 40 lesions (43.0%) were located in the left hemisphere and 53 (57.0%) in the right hemisphere. Sixty-one (65.6%) patients had a fMRI scan. The lesion-to-eloquence distance was less than or equal to 10 mm in 55 of these 61 patients (90.9%). The most common histological diagnoses were glioma (62 patients, 66.7%) and metastasis (18 patients, 19.4%). Pre-existing neurologic deficits were found in 47 patients (50.5%). Thirty patients (32.3%) had a reoperation after tumor recurrence. Detailed characteristics of the (peri-)rolandic brain lesion patients are summarized in **Table 5**.

The second group consisted of 78 CPA lesion patients, consisting of 29 men (37.2%) and 49 women (62.8%), with a mean age of 53.4 ± 14.7 years. There were 43 lesions (55.1%) which were located in the left and 35 lesions (44.9%) which were located in the right CPA. The most common histological diagnoses were schwannoma (40 patients, 51.3%), mostly vestibular schwannoma (33 patients, 82.5%), and grade I meningioma (21 patients, 26.9%). Pre-existing deficits were present in 7 patients (9.0%). Eight patients (10.3%) had a reoperation after tumor recurrence. Detailed characteristics of the CPA lesion patients are summarized in **Table 6**.

There were 67 patients with a spine lesion, including 31 men (46.3%) and 36 women (53.7%) with a mean age 55.1 ± 12.9 years. Twenty-three lesions (34.3%) were intramedullary located and 39 lesions (58.2%) were extramedullary located, including 21 intradural 18 extradural lesions. There were 5 patients (7.5 %) with a tethered cord syndrome. Twenty-five (37.3%) lesions were located at cervical level, 24 lesions (35.8%) at thoracic level and 13 lesions (19.4%) at lumbosacral level. The most common histological diagnosis was ependymoma (8 patients, 11.9%). Fifty patients (74.6%) had pre-existing neurologic deficits and 5 patients (7.5%) had a reoperation after tumor recurrence. Detailed characteristics of the spine lesion patients are summarized in **Table 7**.

There were 6 patients with a PN lesion and 2 patients with a lesion in the fourth ventricle. The small sample size and the absence of irreversible neurologic deterioration in PN lesion patients did not allow further analyses of these patients.

Table 5: Characteristics of the (peri-)rolandic brain lesion patients in the retrospective study (n=93).

Characteristic	Value
Gender	
Female	42 (45.2)
Male	51 (54.8)
Age (years)*	53.5 ± 14.9
Age categories (years)	
16 - 35	13 (14.0)
36 - 55	32 (34.4)
56 - 85	48 (51.6)
Side	
Left	40 (43.0)
Right	53 (57.0)
Histology	
Glioma	62 (66.7)
High grade	51 (54.8)
Low grade	11 (11.8)
Metastasis	18 (19.4)
Lung carcinoma	9 (9.7)
Breast carcinoma	3 (3.2)
Malignant melanoma	2 (2.2)
Colorectal carcinoma	2 (2.2)
Renal cell carcinoma	1 (1.1)
Undefined	1 (1.1)
Other	13 (14.0)
AVM	5 (5.4)
Aneurysm	2 (2.2)
Meningioma	2 (2.2)
Radionecrosis	2 (2.2)
Sarcoma	1 (1.1)
DNET	1 (1.1)
Pre-existing deficits	47 (50.5)
Recurrence	30 (32.3)
Lesion-to-eloquence distance**	
> 10 mm	55 (90.9)
≤ 10 mm	6 (9.8)

*Data are presented as n (%) or *mean ± SD; ** % of cases who had a fMRI scan (61, 65.6%); AVM, arteriovenous malformation; DNET, dysembryoplastic neuroepithelial tumor.*

Table 6: Characteristics of the CPA lesion patients in the retrospective study (n=78).

Characteristic	Value
Gender	
Female	49 (62.8)
Male	29 (37.2)
Age (years)*	53.4 ± 14.7
Age categories (years)	
16 - 35	11 (14.1)
36 - 55	29 (37.2)
56 - 85	38 (48.7)
Side	
Left	43 (55.1)
Right	35 (44.9)
Histology	
Schwannoma	40 (51.3)
n. IV	1 (1.3)
n. V	2 (2.6)
n. VII	2 (2.6)
n. VIII	33 (42.3)
n. IX	2 (2.6)
Meningioma	21 (26.9)
Epidermoid cyst	8 (10.3)
Neurovascular conflict	4 (5.1)
Metastasis	3 (3.8)
Lung carcinoma	2 (2.6)
Breast carcinoma	1 (1.3)
AVM	1 (1.3)
Chondroma	1 (1.3)
Pre-existing deficits	7 (9.0)
Recurrence	8 (10.3)

*Data are presented as n (%) or *mean ± SD; CPA, cerebellopontine angle; AVM, arteriovenous malformation.*

Table 7: Characteristics of the spine lesion patients in the retrospective study (n=67).

Characteristic	Value
Gender	
Female	36 (53.7)
Male	31 (46.3)
Age (years)*	55.1 ± 12.9
Age categories (years)	
26 - 55	34 (50.7)
56 - 85	33 (49.3)
Location	
Intramedullary	23 (34.3)
Extramedullary	39 (58.2)
Intradural	21 (31.3)
Extradural	18 (26.9)
Tethered cord	5 (7.5)
Spinal cord level	
Cervical	25 (37.3)
Thoracal	24 (35.8)
Lumbosacral	13 (19.4)
Tethered cord	5 (7.5)
Histology	
Ependymoma	8 (11.9)
Schwannoma	7 (10.4)
Lateral disc herniation	7 (10.4)
Meningioma	5 (7.5)
Tethered cord	5 (7.5)
Trauma	5 (7.5)
Hemangioblastoma	4 (6.0)
Metastasis	4 (6.0)
Renal cell carcinoma	2 (3.0)
Breast carcinoma	1 (1.5)
Ependymoma	1 (1.5)
AVF	3 (4.5)
Undefined	3 (4.5)
Astrocytoma	2 (3.0)
Hemangioma	2 (3.0)
Arachnoid cyst	1 (1.5)
Dermoid cyst	1 (1.5)
Dura rotation	1 (1.5)
Foreign object	1 (1.5)
Lipoma	1 (1.5)
Lymphoma	1 (1.5)
Meningocele	1 (1.5)
MPNST	1 (1.5)
Osteoblastoma	1 (1.5)
Syringobulbia	1 (1.5)
Syrinx	1 (1.5)
Pre-existing deficits	50 (74.6)
Recurrence	5 (7.5)

Data are presented as n (%) or *mean ± SD; AVF, arteriovenous fistula; MPNST, malignant peripheral nerve sheath tumor.

3.1.2 Rates, type and severity of irreversible postoperative deterioration despite IONM

To determine the rate, type and severity of irreversible postoperative neurologic deterioration despite IONM (number of patients relative to group size), preoperative, short-term postoperative and long-term postoperative outcome data were recorded from clinical reports in every patient group (brain, CPA and spine lesions). In patients with (peri-)rolandic brain lesions (n = 93), CPA lesions (n = 78) and spine lesions (n = 67), no neurologic deterioration after IONM-assisted surgery was observed in 69 patients (74%), 44 patients (56%) and 53 patients (79%) respectively. Reversible neurologic deterioration was observed in 11 patients (12%), in 14 patients (18%) and in 6 patients (9%) respectively. Irreversible neurologic deterioration was observed in 13 patients (14%), in 20 patients (26%) and in 8 patients (12%) respectively (**Figure 5**).

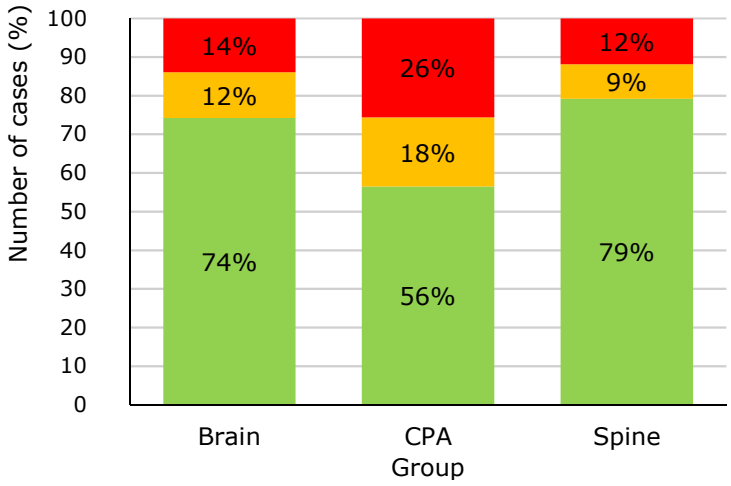

Figure 5: Rates of no, reversible and irreversible postoperative neurologic deterioration in (peri-)rolandic brain lesion, CPA lesion and spine lesion cases. Green bars indicate no deterioration, orange bars indicate reversible deterioration and red bars indicate irreversible deterioration.

In patients with (peri-)rolandic brain lesions, irreversible deterioration consisted of contralateral limb motor (n = 13, 100%) and/or sensory (n = 3, 23.1%) deficits. (**Table 8**). 4 of 13 patients with postoperative (worsening of) contralateral hemiparesis (30.8%) had pre-operative slight muscle weakness (sMRC 2). Only 1 patient (7.7%) had a complete postoperative paralysis (sMRC 0). Six patients (46.2%) had severe muscle weakness (sMRC 1), and another 6 patients (46.2%) had slight muscle weakness (sMRC 2). New postoperative contralateral hypesthesia was reported in only one of the 13 cases with postoperative (worsening of) contralateral hemiparesis (**Table 8**).

In patients with CPA lesions, irreversible deterioration consisted of motor CN deficits (22 cranial nerve palsies in 20 patients) (**Table 9**). 14 of 22 cranial nerve palsies (64%) were facial nerve palsies (6 complete palsies, 4 severe weaknesses, 4 slight weaknesses). The remaining 8 of 22 cranial nerve palsies were reported in n. III (1 case), n. IV (3 cases), n. V (1 case), n. VI (1 case), n. IX (1 case) and n. X (1 case) (1 complete palsy, 5 severe weaknesses, 2 slight weaknesses). Eleven of 22 cranial nerve palsies (50%) were not unexpected, as 3 damaged CNs were identified as the lesion's origin, 3 damaged CNs adhered firmly to the tumor and 5 CNs were intentionally sacrificed to achieve maximal tumor resection (**Figure 6**). Thus, 11 cranial nerve palsies were truly unexpected (n. III,

V, VI and X: 1 case each, n. VII: 7 cases) (**Table 9**). Excluding the cases of predicted cranial nerve palsy, the rate of irreversible postoperative deterioration was 14%.

In patients with spine lesions, irreversible deterioration consisted of bilateral motor and/or sensory deficits (**Table 8**). Four of 8 patients (50.0%) had slight pre-operative muscle weakness (sMRC 2). One patient improved after surgery, while 3 patients had severe postoperative bilateral motor deficits (sMRC 1) Table 8). Four patients (50.0%) had severe and 2 patients (25.0%) had slight postoperative sensory deficits (**Table 8**).

Table 8: Severity of preoperative and postoperative deficits in irreversible deteriorated cases with (peri-)rolandic brain and spine lesions.

	(Peri-)rolandic brain		Spine	
Score	Preop	Postop	Preop	Postop
sMRC				
0	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
1	0 (0.0)	6 (46.2)	0 (0.0)	3 (37.5)
2	4 (30.8)	6 (46.2)	4 (50.0)	0 (0.0)
3	9 (69.2)	0 (0.0)	4 (50.0)	5 (62.5)
Sensory				
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	4 (50.0)
2	2 (15.4)	3 (23.1)	4 (50.0)	2 (25.0)
3	11 (84.6)	10 (76.9)	4 (50.0)	2 (25.0)

Data are presented as n(%); Motor deficits were scored according to the simplified Medical Research Council (sMRC) scale; 0: complete paralysis, 1: severe weakness, 2: slight weakness, 3: normal strength; Sensory deficits were analogously scored; 0: complete deficit, 1: severe deficit, 2: slight deficit, 3: normal function; Postoperative scores were obtained 3 months after surgery.

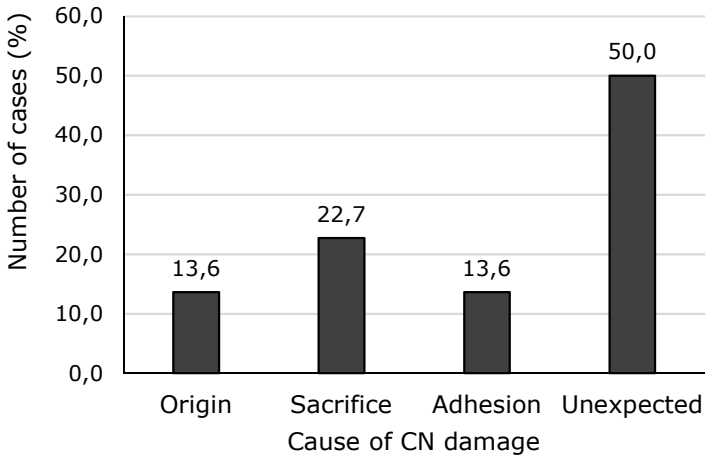

Figure 6: Causes of irreversible cranial nerve damage in CPA lesion patients. CPA, cerebellopontine angle; CN, cranial nerve.

Table 9: Severity of preoperative and postoperative deficits in irreversible deteriorated cases with CPA lesions.

CPA			CPA*		
CN Score	Preop	Postop	CN Score	Preop	Postop
0	0 (0.0)	7 (31.8)	**0**	0 (0.0)	2 (18.2)
n. IV		1	n. III		1
n. VII		6	n. VII		1
1	0 (0.0)	9 (40.9)	**1**	0 (0.0)	5 (45.5)
n. III		1	n. VI		1
n. IV		2	n. VII		4
n. VI		1			
n. VII		4			
n. IX		1			
2	0 (0.0)	6 (27.3)	**2**	0 (0.0)	4 (36.4)
n. V		1	n. V		1
n. VII		4	n. VII		2
n. X		1	n. X		1
3	22 (100.0)	0 (0.0)	**3**	11 (100)	0 (0.0)
n. III	1		n. III	1	
n. IV	3		n. V	1	
n. V	1		n. VI	1	
n. VI	1		n. VII	7	
n. VII	14		n. X	1	
n. IX	1				
n. X	1				

Data are presented as n(%) or n; Scores are presented for all CPA lesion cases (CPA) and for CPA lesion cases with only unexpected postoperative deficits (CPA*); CN palsies were scored analogous to the simplified Medical Research Council (sMRC) scale; 0: complete deficit, 1: severe deficit, 2: slight deficit, 3: normal function; Postoperative scores were obtained 3 months after surgery.

3.1.3 Patient and lesion characteristics related to irreversible deterioration

Patient and lesion characteristics were correlated with the risk of irreversible postoperative deterioration in patients with (peri-)rolandic brain, CPA, and spine lesions, using univariate logistic regression (**Table 10, 11 and 12**). This analysis allowed the identification of those characteristics predictive for irreversible neurologic deficits after IONM-assisted surgery. In (peri-)rolandic brain lesion patients, lesion recurrence (P=0.003) was significantly correlated with irreversible deterioration (**Table 10**). As no patients with no high risk lesion (lesion-to-eloquence distance > 10 mm) had irreversible postoperative deficits, logistic regression could not be performed (no variability). In CPA lesion patients, male gender (P=0.0155) and schwannomas (P=0.0329) were significantly related to irreversible deterioration (**Table 11**). When excluding the cases of expected CN palsies, only male gender was significantly correlated with irreversible deterioration (P=0.0357). As no patients with preoperative deficits had irreversible postoperative worsening of deficits, logistic regression could not be performed (no variability). In spine lesion patients, intramedullary location (P=0.013) was significantly correlated with irreversible deterioration (**Table 12**). As no patients with recurrent spine lesions had irreversible postoperative deficits, logistic regression could not be performed (no variability).

Table 10: Patient and lesion characteristics of irreversible deteriorated (peri-)rolandic brain lesion cases.

Characteristic	%	P value
Gender (male/female)	13.7/14.3	0.9382
Age (years)		0.9535
16 - 35	12.5	
36 - 55	12.5	
56 - 85	14.6	
Side (left/right)	17.5/11.3	0.3973
Histology		0.1500
Glioma	12.9	
Metastasis	5.6	
Other	15.4	
Pre-existing deficits (yes/no)	12.8/15.2	0.7331
Recurrence (yes/no)	30.0/6.3	0.0030
Lesion-to-eloquence distance (≤10mm/>10mm)	16.4/0.0	-

% values are probabilities of irreversible postoperative deterioration; Data were analyzed by univariate logistic regression; significance level P<0.05.

Table 11: Patient and lesion characteristics of irreversible deteriorated CPA lesion cases.

Characteristic	%	P value
Gender (male/female)	41.4/16.3	0.0155
Age (years)		0.6021
16 - 35	36.4	
36 - 55	20.7	
56 - 85	26.3	
Side (left/right)	23.3/28.6	0.5934
Histology		0.0329
Schwannoma	37.5	
Meningioma	9.5	
Other	17.6	
Pre-existing deficits (yes/no)	0.0/28.2	-
Recurrence (yes/no)	12.5/27.1	0.3367

% values are probabilities of irreversible postoperative deterioration; Data were analyzed by univariate logistic regression; Significance level P<0.05;.CPA, cerebellopontine angle.

Table 12: Patient and lesion characteristics of irreversible deteriorated spine lesion cases.

Characteristic	%	P value
Gender (male/female)	9.7/13.9	0.5978
Age (years)		0.4226
16 - 55	8.8	
56 - 85	15.2	
Location (intra/extra*)	26.1/5.1	0.0130
Spinal level		0.0923
Cervical	24.0	
Thoracal	4.2	
Lumbosacral	7.2	
Histology		0.2706
Ependymoma	25.0	
Other	10.5	
Pre-existing deficits (yes/no)	14.0/5.9	0.3413
Recurrence (yes/no)	0.0/12.9	-

*Intramedullary/extramedullary; % values are probabilities of irreversible postoperative deterioration; Data were analyzed by univariate logistic regression; Significance level P<0.05.

3.1.4 Prediction model versus intuition model

A prediction model, based on the patient- and lesion-related characteristics significantly correlating with irreversible deficit, was compared with an intuition model, based on the characteristics supposed to correlate with irreversible deficit according to expert opinion. The characteristics incorporated in both models and the accompanying BIC values are summarized in **Table 13**. For (peri-)rolandic brain lesion patients, the prediction model consisted of the factor 'tumor recurrence'. The intuition model included 'pre-existing neurologic deficits', 'histology' and 'tumor recurrence' (BIC value 83.5). For CPA lesion patients, the prediction model was built of 'gender' and 'histology' (BIC value 93.6). The intuition model included 'histology' and 'tumor recurrence' (BIC value 99.2). For spine lesion patients, the prediction model was consisted of 'lesion location' (BIC value 50.4). The intuition model included 'pre-existing deficits', 'lesion location', 'spinal level' and 'histology' (BIC value 63.8).

'Lesion-to-eloquence distance' (brain lesions), 'pre-existing deficits' (CPA lesions) and 'tumor recurrence' (spine) were also indicated as relevant but were not included in the intuitions models due to insufficient variability (see section 3.1.3.).

Taken together, these results demonstrate that the BIC values of the prediction models were lower than the BIC values of the intuition models. Thus, the prediction models seem to better predict irreversible postoperative deterioration in patients with (peri-)rolandic brain, CPA and spine lesions than the intuition models.

Table 13: Prediction and intuition models for irreversible deterioration in cases with (peri-)rolandic brain, CPA and spine lesions.

Group	Prediction	BIC value	Intuition	BIC value
Brain	Recurrence	75.5	Pre-existing deficits Histology Recurrence	83.5
CPA	Gender Histology	93.6	Histology Recurrence	99.2
Spine	Lesion location	50.4	Pre-existing deficits Lesion location Spinal level Histology	63.8

BIC, Bayesian information criterion.

3.2 Prospective observational pilot study

The prospective observational study analyzed the relationship between IONM parameters and postoperative neurologic outcome in an explorative way. First, patient and lesion characteristics are described. Second, the rates, type and severity of postoperative neurologic deterioration are presented. Third, the course of absolute amplitude and latency over resection time was examined in order to determine the best options for calculating amplitude and latency changes in tMEPs, D-waves and SSEPs. Finally, relative amplitude and latency changes were correlated with differences in preoperative and postoperative clinical scores in tMEPs, D-waves and SSEPs. Success of mapping was related to irreversible postoperative deterioration in EMG, DCS and DSCS. In DSCS, motor thresholds were correlated with differences in MRC scores as well.

3.2.1 Patient and lesion characteristics

A total of 32 consecutive surgeries in 30 patients (mean age 55.2 years, range 7-87 years; 16 men, 16 women) were included in the study after obtaining informed consent. Two patients had two operations during the study period. One patient with a giant CPA lesion was treated by debulking from two different points of access. One patient with a spinal lesion needed reoperation because of insufficient tumor debulking after the first procedure. The first group consisted of 14 (43.8%) patients with (peri-)rolandic brain lesions, 8 located in the left and 6 in the right hemisphere. These lesions consisted of 6 high grade gliomas (4 recurrences), 1 low grade glioma, 4 metastases (3 lung carcinomas including 1 recurrence, 1 cervix carcinoma), 1 nocardial brain abscess, 1 ganglioglioma and 1 diffuse large B-cell lymphoma (DLBCL). The lesion-to-eloquence distance was less or equal to 10 mm in 11 cases and more than 10 mm in 3 cases. The second group consisted of 10 (30.0%) patients with CPA lesions, 6 located in the right and 4 in the left CPA. These lesions included 6 schwannomas (4 n. VIII, 1 n. VII, 1 undetermined), 2 meningiomas (grade I), 1 recurrent epidermoid cyst and 1 dolichoectatic basilar artery. The third group consisted of 8 (24.2%) patients with spine lesions, which were all intradural (5 intramedullary, 3 extramedullary; 1 cervical, 5 thoracic, 2 lumbosacral). These lesions included 3 metastases (2 breast carcinomas, 1 malignant melanoma), 2 cavernous angiomas, 1 meningioma, 1 schwannoma (root S1) and 1 myelocele. Patient characteristics are summarized in **Table 14, 15 and 16**.

Table 14: Characteristics of the (peri)rolandic brain lesion patients in the prospective study (n=14).

Characteristic	Value
Gender	
Female	4 (28.6)
Male	10 (71.4)
Age (years)*	56.2 (7-87)
Side	
Left	8 (57.1)
Right	6 (42.9)
Histology	
Glioma	
High grade	6 (42.9)
Low grade	1 (7.1)
Metastasis	
Lung carcinoma	3 (21.4)
Cervix carcinoma	1 (7.1)
Nocardial brain abscess	1 (7.1)
Ganglioglioma	1 (7.1)
DLBCL	1 (7.1)
Recurrence	5 (35.7)
Lesion-to-eloquence distance	
> 10 mm	3 (21.4)
≤ 10 mm	11 (78.6)

Data are presented as n (%) or *mean (range); DLBCL, diffuse large B-cell lymphoma.

Table 15: Characteristics of the CPA lesion patients in the prospective study (n=10).

Characteristic	Value
Gender	
Female	5 (50.0)
Male	5 (50.0)
Age (years)*	52.0 (25-74)
Side	
Left	4 (40.0)
Right	6 (60.0)
Histology	
Schwannoma	
n. VIII	4 (40.0)
n. VII	1 (10.0)
Undetermined	1 (10.0)
Grade I meningioma	2 (20.0)
Epidermoid cyst	1 (10.0)
Dolichoectatic basilar artery	1 (10.0)
Recurrence	1 (10.0)

Data are presented as n (%) or *mean (range); CPA, cerebellopontine angle.

Table 16: Characteristics of the spinal lesion patients in the prospective study (n=8).

Characteristic	Value
Gender	
Female	7 (87.5)
Male	1 (12.5)
Age (years)*	57.5 (45-87)
Location	
Intramedullary	5 (62.5)
Extramedullary	3 (37.5)
Spinal level	
Cervical	1 (12.5)
Thoracic	5 (62.5)
Lumbosacral	2 (25.0)
Histology	
Metastasis	
Breast carcinoma	2 (25.0)
Malignant melanoma	1 (12.5)
Cavernous angioma	2 (25.0)
Meningioma	1 (12.5)
Schwannoma root S1	1 (12.5)
Myelocele	1 (12.5)

Data are presented as n (%) or *mean (range).

3.2.2 Rates, type and severity of postoperative deterioration

Postoperative deterioration, consisting of contralateral hemiparesis, was observed in 6 out of 14 patients with (peri-)rolandic brain lesions (**Table S1**; procedures 10, 14, 18, 23, 26, 32). The worst deterioration was observed in procedure 14. This was a reoperation in a patient with a recurrent right frontal glioblastoma multiforme. Postoperative deterioration occurred in another 4 patients with pre-operative deficits. One patient with a new diagnosis of a low grade glioma, had a mild postoperative paresis of the contralateral upper limb. The single patient in whom SSEPs were monitored, had no deterioration of contralateral limb sensation (data not shown).

Only one patient with a CPA lesion had a postoperative CN palsy (FN) (**Table S2**). In this patient, the CN had been identified by triggered EMG, but was intentionally sacrificed in order to proceed with the operation.

Four out of 8 spinal surgeries were complicated by postoperative deterioration, consisting of paraparesis (procedures 22, 31 and 34) or tetraparesis (procedure 33) (**Table S3**). The worst deterioration was observed in the patient with an intramedullary metastasis, who had a pre-existing paraparesis and in whom 2 surgeries were needed to remove the lesion (**Table S3**; procedures 31 and 34). SSEPs were monitored in 5 patients (4 intramedullary lesions, 1 extramedullary lesion). Sensation deteriorated in 3 out of 4 patients with an intramedullary lesion (data not shown).

3.2.3 Course of absolute amplitude and latency over resection time

As a first step in finding correlations between IONM parameters and neurologic outcome, the raw amplitude and latency data of tMEPs, D-waves and SSEPs in patients with (peri-)rolandic brain lesions and spinal lesions were plotted over resection time. **Figure 6** presents the course of absolute tMEP amplitude and latency recorded in the tibialis anterior muscle during resection of (peri-)rolandic brain lesions in 10 patients.

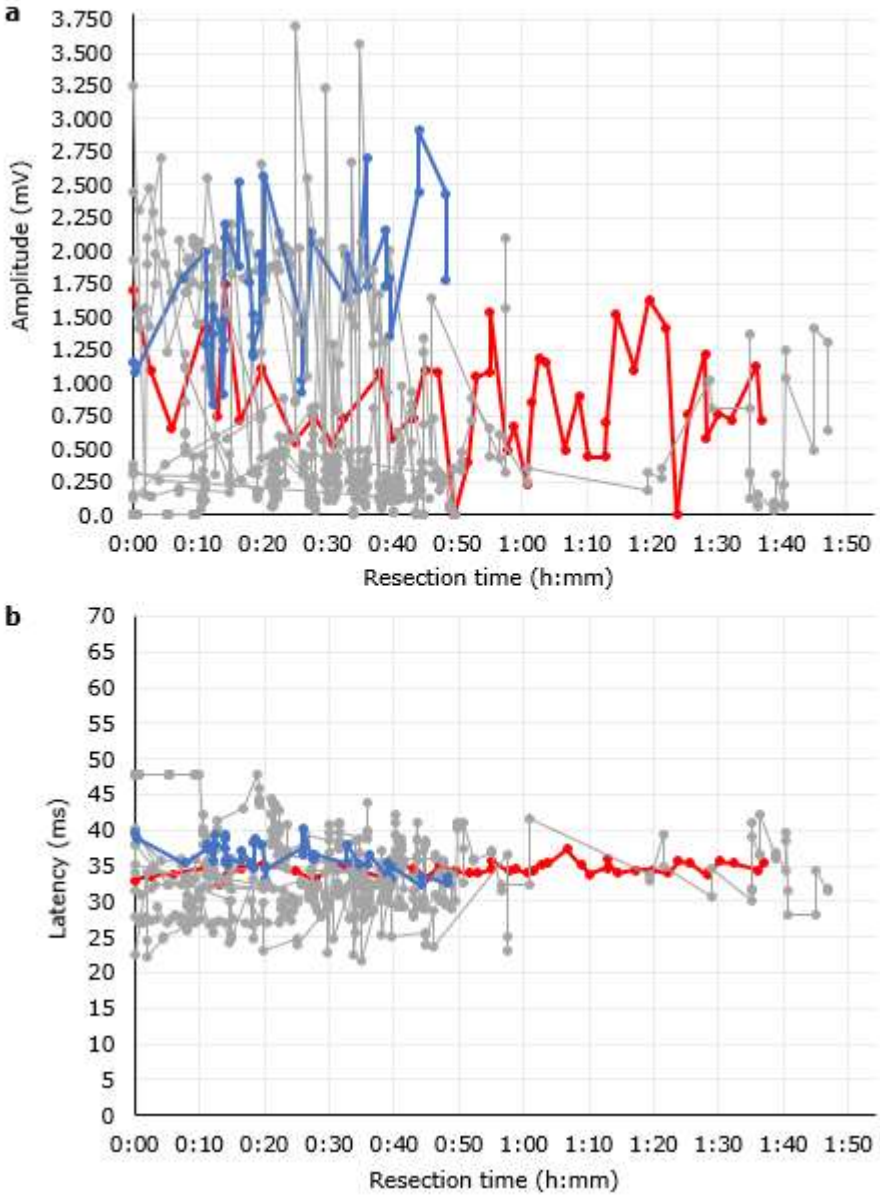

Figure 6: Course of absolute tMEP amplitude and latency recorded in the tibialis anterior muscle during resection of (peri-)rolandic brain lesions. Data are from ten (peri-)rolandic brain lesion patients with successful tMEPs in the (left or right) tibialis anterior muscle; Case 1 is presented in blue; Case 2 is presented in red; tMEP monitoring was initiated at the start of lesion resection and finalized after removal of the lesion; **a:** The absolute amplitude (millivolts) of tMEPs in the tibialis anterior muscle shows a high trial-to-trial variability within and between case 1 and 2. An incremental effect can be observed in both cases after multiple consecutive stimuli within seconds; **b:** The absolute latency (miliseconds) of tMEPs in the tibialis anterior muscle of both cases shows a very low intra- and interpatient trial-to-trial variability and no incremental effect after multiple consecutive stimuli.

tMEP amplitudes in case 1 (highlighted in blue) were more elevated than in case 2 (highlighted in red) (Figure 6a). Amplitudes ranged from 0.836 mV to 2.912 mV in case 1 and from 0 mV to 1.746 mV in case 2. Furthermore, amplitudes often tended to increase after multiple consecutive stimulations, as observed in case 1 (19 minutes after start of resection) and in case 2 (1 hour and 14 minutes after start of resection). These results were also observed in tMEP amplitudes recorded in the tibialis anterior muscle of spine lesion patients (**Figure S1a**) and all other recorded muscles in both patients with (peri-)rolandic brain lesions and spine lesions (data not shown).

Latencies of tMEPs recorded in the tibialis anterior muscle in case 1 and 2 were of comparable length and decreasing latencies were rarely observed after multiple consecutive stimuli (**Figure 6b**). Equivalent results were observed in tMEP latencies recorded in the tibialis anterior muscle of spine lesion patients (**Figure S1b**) and all other recorded muscles in both patients with (peri-)rolandic brain lesions and spine lesions (data not shown).

These data demonstrate a high intra- and interpatient trial-to-trail variability in tMEP amplitudes in contrast to tMEP latency. Furthermore, there is an incremental effect on tMEP amplitudes after multiple consecutive stimuli within seconds.

3.2.4 Amplitude and latency change of tMEPs related to motoric outcome

To determine whether tMEP amplitude and latency could be correlated with motoric outcome after surgery, several statistical analyses were performed using univariate mixed models for (peri-)rolandic brain lesions and spine lesion patients.

Table 17: Correlation of changes in tMEP parameters and differences in MRC scores in (peri-)rolandic brain lesion cases.

	ΔMRC score preop - ST postop		ΔMRC score ST postop – LT postop	
tMEP parameter	P values distal muscles	P values proximal muscles	P values distal muscles	P values proximal muscles
ΔAmp				
Average	0.5934	0.8341	0.9986	0.9991
Median	0.6743	0.9210	0.9986	0.9993
Best	0.7142	0.4470	0.9986	0.9990
ΔLat				
Average	0.1178	0.6084	0.9988	0.9950
Median	0.2016	0.4174	0.9980	0.9992
Best	0.8768	0.8773	0.9995	0.9992

Change in average, median and best amplitude (ΔAmp) and latency (ΔLat) within the first and last 5 minutes of resection were quantified by ΔAmp = (Amp_{start}–Amp_{end})/Amp_{start} and ΔLat = (Lat_{start}–Lat_{end})/Lat_{start} respectively; Data were analyzed using univariate mixed models for change amplitude and latency; Significance level $P<0.05$; tMEP, transcranial motor evoked potential; MRC, Medical Research Council; ST postop, short-term postoperative; LT postop, long-term postoperative; preop, preoperative.

From the total of 56 recordings in 14 (peri-)rolandic brain lesion patients, 11 recordings in 5 patients were excluded because of failure to obtain tMEPs due to severe preoperative paresis. In the remaining 45 recordings (13 patients), no significant correlations could be found between amplitude change and differences (ΔMRC score) in preoperative and short-term postoperative MRC scores nor between amplitude change and short-term versus long-term postoperative ΔMRC scores (**Table 17**).

Similarly, there were no significant correlations between latency change and differences (ΔMRC score) in preoperative and short-term postoperative MRC scores nor between amplitude change and short-term and long-term postoperative ΔMRC scores (**Table 17**).

From the total of 50 recordings in 8 spine lesion patients, 10 recordings in 3 patients were excluded because of failure to obtain tMEPs due to severe preoperative paresis. Two recordings (left and right biceps muscles of 1 patient) failed due to overweight. In the remaining 38 recordings (8 patients), borderline significant correlations could be found between 1) amplitude change (average, median, best) and ΔMRC score in preoperative versus short-term postoperative scores for the proximal muscles (P=0.0676, P=0.0393 and P=0.0563 respectively); 2) between amplitude change (median) and ΔMRC score in short-term versus long-term postoperative scores for distal muscles; and 3) between latency change (best) and ΔMRC scores in preoperative versus short-term postoperative scores for proximal muscles (**Table 18**). No analyses could be performed to reveal a correlation between ΔLat and ΔAmp and ΔMRC scores in short-term versus long-term postoperative scores for proximal muscles, as only 2 patients met these conditions (too small sample size).

Table 18: Correlation of changes in tMEP parameters and differences in MRC scores in spine lesion cases.

	ΔMRC score Preop - ST postop		ΔMRC score ST postop – LT postop	
tMEP parameter	P values distal muscles	P values proximal muscles	P values distal muscles	P values proximal muscles
ΔAmp				
Average	0.5395	0.0676	0.1335	-
Median	0.6385	0.0396	0.0628	-
Best	0.6240	0.0563	0.2234	-
ΔLat				
Average	0.4373	0.2156	0.5456	-
Median	0.4409	0.2182	0.9470	-
Best	0.8261	0.0479	0.1370	-

Change in average, median and best amplitude (ΔAmp) and latency (ΔLat) within the first and last 5 minutes of resection were quantified by ΔAmp = (Amp_{start}–Amp_{end})/Amp_{start} and ΔLat = (Lat_{start}–Lat_{start})/Lat_{end} respectively; Data were analyzed using univariate mixed models for change in amplitude and latency; Significance level P<0.05; tMEP, transcranial motor evoked potential; MRC, Medical Research Council; ST postop, short-term postoperative; LT postop, long-term postoperative; preop, preoperative.

Parameter estimates for ΔMRC scores of the aforementioned significant models are presented in **Table 19**. Change in amplitude (average, median and best) was inversely correlated with difference in preoperative and short-term postoperative MRC scores in proximal muscles. Change in amplitude was also inversely proportional to the difference in short-term versus long-term postoperative MRC scores in distal muscles. This means that the higher ΔAmp, the lower ΔMRC scores. In contrast, change in latency (best) was directly correlated with difference in preoperative versus short-term postoperative MRC scores in proximal muscles; Thus, the higher ΔLat, the higher ΔMRC scores. These results indicate that muscle strength will improve in proximal muscles directly after surgery, when amplitude was decreased at the end of resection. Muscle strength will further improve in distal muscles 3 months after surgery. When latency was increased at the end of resection, muscle strength will deteriorate in proximal muscles directly after surgery.

Table 19: Parameter estimates for change in amplitude and latency related to ΔMRC scores in spine lesion cases.

	Estimate	
Parameter	Preop - ST postop Proximal muscles	ST postop – LT postop Distal muscles
ΔAmp		
Average	-0.0052	-
Median	-0.0056	-0.0346
Best	-0.0063	-
ΔLat		
Best	0.0336	-

Change in average, median and best amplitude (ΔAmp) and latency (ΔLat) within the first and last 5 minutes of resection were quantified by ΔAmp = $(Amp_{end}–Amp_{start})/Amp_{end}$ and ΔLat = $(Lat_{end}–Lat_{start})/Lat_{end}$ respectively; Data were analyzed using univariate regression; tMEP, transcranial motor evoked potential; MRC, Medical Research Council; ST postop, short-term postoperative; LT postop, long-term postoperative; preop, preoperative.

3.2.5 Amplitude and latency change of D-waves related to motoric outcome

To determine whether D-waves amplitude and latency change could be correlated with motoric outcome after surgery in spine lesion patients, several statistical analyses were performed using univariate regression.

Table 20: Correlation of changes in D-wave parameters and differences in MRC scores in spine lesion cases.

	ΔMRC score Preop- ST postop	
D-wave parameter	P values distal muscles	P values proximal muscles
ΔAmp		
Average	1.0	1.0
Median	0.4	0.4
Best	1.0	1.0
ΔLat		
Average	0.2	0.2
Median	0.2	0.2
Best	0.6	0.6

Change in average, median and best amplitude (ΔAmp) and latency (ΔLat) within the first and last 5 minutes of resection were quantified by ΔAmp = (Ampstart–Ampend)/ Ampstart and ΔLat = (Latstart–Latend)/Latstart respectively; Data were analyzed using Spearman correlation; Significance level $P<0.05$; tMEP, transcranial motor evoked potential; MRC, Medical Research Council; ST postop, short-term postoperative; preop, preoperative.

D-waves were performed in 4 spine lesion patients. Because of this small sample size, a non-parametric test (Spearman correlation) has been used to analyze these data. No significant correlations could be found between amplitude change and ΔMRC score in preoperative versus short-term postoperative scores (**Table 20**).

3.2.6 Amplitude and latency change of lower limb SSEPs related to sensory outcome

To determine whether lower limb SSEP amplitude and latency change could be correlated with sensory outcome after surgery in spine lesion patients, several statistical analyses were performed using univariate mixed models.

Lower limb SSEPs were recorded in 5 of the 8 spine lesion patients (10 recordings). Three recordings in 2 patients were excluded because of failure to obtain lower limb SSEPs due to severe preoperative sensory deficits. In the remaining 7 recordings (4 patients), no significant correlations could be found between amplitude change and differences in preoperative versus short-term postoperative scores (**Table 21**). No correlation analysis could be performed for amplitude change and differences in short-term versus short-term postoperative sensory scores, as the time frame of this study did not allow clinical examination three months after surgery. Spearman correlation of left and right SSEPs separately showed no results, due to the small sample size.

Table 21: Correlation of changes in SSEP parameters and differences in sensory scores in spine lesion cases.

Lower limb SSEP parameter	P values ST postop - preop
ΔAmp	
Average	0.9064
Median	0.8437
Best	0.9665
ΔLat	
Average	0.1540
Median	0.1596
Best	0.2080

Change in average, median and best amplitude (ΔAmp) and latency (ΔLat) within the first and last 5 minutes of resection were quantified by $\Delta Amp = (Amp_{start} - Amp_{end})/Amp_{start}$ and $\Delta Lat = (Lat_{start} - Lat_{end})/Lat_{start}$ respectively; Data were analyzed using univariate mixed models; Significance level $P<0.05$; tMEP, transcranial motor evoked potential; MRC, Medical Research Council; ST postop, short-term postoperative; preop, preoperative.

3.2.7 Success of mapping in DCS and DSCS related to motoric outcome

To determine whether successful mapping of the PMC (DCS) and of the CST (DSCS) could be correlated with motoric outcome after surgery in (peri-)rolandic brain lesion patients, several statistical analyses were performed using univariate mixed models.

DCS was performed in 8 of the 14 (peri-)rolandic brain lesions patients (32 recordings). Successful mapping of the PMC was not correlated with ΔMRC score in preoperative versus short-term postoperative scores (**Table 22**). No statistical analysis could be performed for the relation between successful mapping and ΔMRC score in short-term versus long-term postoperative, as the patients who had a clinical examination after 3 months had a ΔMRC of 0 (no variability).

DSCS was performed in 11 of the 14 (peri-)rolandic brain lesions patients (44 recordings). Successful mapping of the CST was significantly correlated with ΔMRC score in preoperative versus short-term postoperative and short-term versus long-term postoperative scores (**Table 22**). Muscle thresholds

were not correlated with ΔMRC score in preoperative versus short-term postoperative scores and short-term versus long-term postoperative scores (**Table 22**).

Table 22: Correlation of cortical and subcortical mapping and differences in MRC scores in (peri-)rolandic brain lesion cases.

	P values	
Parameter	ΔMRC score ST postop - preop	ΔMRC score LT postop – ST postop
DCS		
Mapping	0.2823	-
DSCS		
Mapping	0.0038	<0.0001
Muscle threshold	0.1415	0.9986

Data were analyzed using univariate mixed models; Significance level P<0.05; The muscle threshold was defined as the minimal stimulation intensity (mA) at which a MEP could be elicited; DCS, direct cortical stimulation; DSCS, direct subcortical stimulation; MRC, Medical Research Council; ST postop, short-term postoperative; LT postop, long-term postoperative; preop, preoperative.

3.2.8 Success of mapping in EMG related to cranial nerve outcome

To determine whether successful mapping of CNs with EMG could be correlated with CN outcome after surgery in CPA lesion patients, several statistical analyses were performed using univariate mixed models.

EMG was performed in 29 recordings of 10 CPA lesion cases. No statistical analysis could be performed for the relation between successful CN mapping and differences in CN palsy scores, because these was not enough variability in the data.

4. Discussion

The retrospective study revealed that the rates of irreversible neurologic deterioration despite IONM-assisted neurosurgery in patients with (peri-)rolandic brain, CPA and spine lesions were 14%, 26% and 12% respectively. These rates illustrate that IONM does not exclude the risk of postoperative irreversible deterioration in the monitored modalities.

In (peri-)rolandic brain lesion patients, postoperative deficits were all motoric. The emphasis of clinical neurologic examination is on muscle strength. Sensation and sensory deficits were often not mentioned in reports, which explains the low rate of these deficits in (peri-)rolandic brain lesion patients. Muscle strength was scored according to broad categories (sMRC), as most clinical reports did not allow more detailed scoring. It is clear from these scores that postoperative deterioration did rarely mean a complete contralateral hemiplegia, as only one case was observed with complete paralysis. The risk of postoperative (worsening of) contralateral paresis was highest in the cases who had a reoperation after tumor recurrence. To our knowledge, this correlation has not been reported before, as current literature on outcome in IONM-assisted (peri-)rolandic brain lesions focuses on patients with a new diagnosis of glioma, without pre-operative neurological deficits (48).

In CPA lesion patients, not all postoperative CN deficits were facial nerve palsies. Severity scores of postoperative deficits indicated that irreversible deterioration did not by definition mean a complete cranial nerve palsy in all cases. The risk of postoperative (worsening of) CN palsy was highest in men and in cases with a schwannoma, as compared to meningioma or other lesions. This high deterioration risk in men is probably due to the high proportion of schwannoma diagnoses in men observed in this study, rather than gender-related influences such as hormones. To our knowledge, these correlations have not been reported before. The current literature on cranial nerve monitoring is almost exclusively dedicated to the facial nerve in vestibular schwannomas (60).

In spine lesion cases, both motor and sensory deficits were observed. The postoperative motor deficit rate was rather low and did not by definition mean a complete para- or tetraplegia. Most cases with postoperative deterioration had sensory deficits. As the lesions were located intramedullary, posterior myelotomy prior to exposure of the lesion is the probable cause of damage to the dorsal column – medial lemniscal pathway. This is also in line with the highest risk of postoperative (worsening of) bi- or tetraparesis and sensory deficits in the cases with intramedullary located lesions.

In the retrospective chart review, multiple cases were observed with postoperative deficits in non-monitored modalities, which can also highly impair QoL. These deficits occurred in modalities not eligible as well as in modalities eligible for IONM. In the latter cases, time pressure was the main reason to select a limited IONM setup. Several patients with (peri-)rolandic brain lesions developed postoperative personality changes (e.g. apathy and irritability), cognitive disorders (e.g. frontal executive dysfunction), psychological symptoms (e.g. mood disorders) epilepsy, hemicorporal pain, coordination disorders or speech disorders. These modalities cannot be monitored in anesthetized patients. Even in awake craniotomy, only a summary evaluation of cognition and speech is possible. Other patients with (peri-)rolandic brain lesions, whose neurosurgery was assisted by only tMEP, had postoperative hemisensory deficits. These cases had a postoperative deficit in a modality that could have been monitored by SSEP. Time pressure in neurosurgical practice often imposes preference of

monitoring motor pathways only over the combination of motor and sensory pathways, as muscle strength is considered more relevant to QoL than sensation. Furthermore, tMEPs and dMEPs are readily acquired, as stimulation and recording requires approximately 1 second, in contrast to SSEPs, in which averaging of 100 stimuli of the median nerve and 150 stimuli of the tibial nerve requires 20 and 40 seconds respectively. Moreover, SSEP recording is easily influenced by technical artefacts. Some patients with CPA lesions had postoperative facial hypesthesia. Facial sensation is mediated by the sensory branches of the trigeminal nerve and cannot be monitored in anesthetized patients. Postoperative hearing loss was reported in several patients with a vestibular schwannoma. Monitoring of the acoustic nerve by way of brainstem auditory evoked potentials (BAEP) is not systematically performed, as time pressure does not allow repeated BAEP recording (averaging of 2000 stimuli requiring several minutes). The clinical reports mentioned dysphagia in certain patients with large CPA lesions. Unfortunately, CN monitoring was limited to the facial and hypoglossal nerves, but did not systematically include the vagus nerve, which requires intubation with a built-in electrode. Some patients with intramedullary spinal cord tumors had postoperative gait disorders despite stable tMEP's and D-waves. They probably had a gait ataxia, caused by dorsal column damage in the obligatory dorsal myelotomy in these procedures.

The postoperative outcome in IONM-assisted neurosurgery can be improved by lessons learnt from the retrospective study. In (peri-)rolandic brain lesion patients, the risk of contralateral motor and sensory deficits can be reduced by the systematic application of multimodal IONM. The modality to map and monitor the pyramidal tract must be in line with each separate step in the surgical procedure. DCS is important to delineate a safe entry zone (i.e. to avoid incision in eloquent motor cortex). tMEPs are needed for continuous monitoring during tumor resection. DSCS is essential to assess the proximity of the pyramidal tract, when reaching the tumor margin. Repeated recording of SSEPs should be implemented systematically, despite the time investment. In CPA lesion patients, the risk of CN palsy can be reduced by the maximal delineation of the course of the CN proximal, adjacent and distal to the lesion. It is important to intensify stimulation to 1 mA before considering CN mapping as negative, as a cranial nerve can adhere to non-nervous fibrous bands. Especially in large CPA lesions, monitoring of the vagus nerve must be included in the setup to prevent postoperative dysphagia. In patients with intramedullary spinal cord tumors, where posterior myelotomy is needed to reach the tumor, the occurrence of postoperative gait ataxia could be prevented by performing dorsal column mapping before proceeding to myelotomy. In all cases, improvement of postoperative neurologic outcome must prevail over time pressure.

To improve postoperative outcome in future IONM-assisted neurosurgeries, we aimed to establish center specific warning criteria for tMEPs, D-waves and SSEPs. We examined whether and how IONM parameter changes can be correlated with neurologic outcome in patients with (peri-) rolandic brain, CPA and spine lesions in a prospective observational pilot study.

The course of absolute amplitude over resection time demonstrated high intra- and interpatient trial-to-trial variability and an incremental effect after multiple consecutive stimuli. The high intra- and interpatient trial-to-trial variability is a known feature of tMEPs and is probably caused by the variable activation of higher (brain) and lower (spinal cord) motor neurons (58). The incremental effect is characterized by initial absent or low amplitude muscle response, followed by gradually increasing

tMEP amplitudes. The reason for this phenomenon is not entirely clear. Possible explanations could be: 1) hyperpolarization of the stimulated cortical regions in time, requiring more trials to depolarize the higher motor neurons; 2) progressive recruitment of several motor systems in addition to the CST (28). As we found no detailed descriptions of how latency, amplitude nor of how changes of these parameters were measured in previous publications on electrophysiological-clinical correlations, nor of how to rule out this amplitude variability in correlation analyses, we calculated baseline and end stage amplitude in three different ways: 1) the average and 2) the median tMEP amplitude, as well as 3) the single best tMEP amplitude of the first 5 minutes after onset of tumor resection and the last 5 minutes of resection. The interval of 5 minutes was long enough to include a sufficient number of trials but short enough to exclude amplitude change caused by surgical damage of the motor tract. Baseline was set at the start of tumor resection, not after placement of electrodes, in order to eliminate possible amplitude changes due to manipulation during craniotomy (rolandic brain and CPA lesions) or laminectomy (spine lesions). The end of monitoring was set at the end of tumor resection, not at wound closure, for similar reasons.

In (peri-)rolandic brain lesion patients, tMEP amplitude and latency changes were not significantly correlated with contralateral hemiparesis. In spine lesion patients, SSEP amplitude and latency changes were not significantly correlated with contralateral sensory deficit. D-wave amplitude and latency changes were not significantly correlated with postoperative paraparesis. These negative results were probably due to the small sample size of the several groups and, more importantly, the insufficient variability within the data.

In spine lesion patients, borderline significant correlations between tMEP amplitude and latency changes and postoperative paraparesis were observed. However, these correlations were contradictory to our expectations, as parameters estimates indicated that 1) short term postoperative proximal muscle strength and long term distal muscle strength improved with amplitude decrease at the end of resection and 2) short term postoperative proximal muscle strength improved with latency increase at the end of resection. The electrophysiological-clinical correlations described by previous authors would predict muscle strength deterioration after tMEP amplitude decrease and tMEP latency increase (32). Our results suggest that additional factors affect correlations between IONM parameter changes and neurologic outcome, such as age, reoperation after tumor recurrence and pre-existing deficits, all influencing revalidation potential, as well as lesion histology. The correlation models must be adjusted for these factors, requiring bigger sample sizes. Other factors affecting electrophysiological-clinical correlations could be changes in stimulation intensity, anesthetic factors (duration of anesthesia and total anesthetic doses) and systemic factors (systolic blood pressure, body temperature). These factors should be systematically recorded during the tumor resection.

There was no significant correlation between success or failure of mapping PMC (DSC) and contralateral hemiparesis in (peri-)rolandic brain lesion patients. There was no significant correlation between success or failure of mapping cranial nerves (triggered EMG) and postoperative CN palsy in CPA lesion patients. The lack of correlation was due to insufficient variability in the data. A significant correlation was found between success or failure of mapping the CST (DCSC) and contralateral hemiparesis. However, the reliability of this correlation is questionable, as sample sizes were small.

In summary, no sound and reliable electrophysiological (IONM parameters) – clinical (postoperative deterioration) correlations were found. Consequently, no center-specific warning criteria for irreversible postoperative deterioration despite IONM-assisted neurosurgery could be established.

At this stage, a strict quantitative approach of electrophysiological and clinical correlations is not possible, reflecting the complex and multifaceted nature of intraoperative neuromonitoring and postoperative clinical outcome. However, a qualitative approach reveals a promising picture of postoperative outcome in IONM-assisted neurosurgery. This is the first prospective study with detailed preoperative and short-term postoperative scoring of limb muscle strength, limb sensation and CN function in patients with (peri-)rolandic brain lesions, CPA lesions and spine lesions. Of the 14 patients with a (peri-)rolandic brain lesion, 5 cases of postoperative deterioration occurred in patients with a pre-existing deficit and/or a reoperation. In the retrospective study, there was no significant correlation of pre-existing deficits and the occurrence of irreversible postoperative deficit in patients with (peri-)rolandic brain lesions. The worst deterioration was observed in a case with reoperation because of a recurrent right frontal glioblastoma multiforme. This observation is in line with the significant correlation of reoperation and occurrence of irreversible postoperative deficit in patients with (peri-)rolandic brain lesions in the retrospective study. The single treatment naive and preoperative intact case with postoperative deterioration, had a mild postoperative paresis (no complete paralysis) of the contralateral upper limb. The only cranial nerve palsy was intentional, in order to proceed with the operation. Four out of 8 spinal surgeries were complicated by postoperative deterioration. The worst deterioration was observed in the patient with an intramedullary metastasis, who had a pre-existing paraparesis and in whom 2 surgeries were needed to remove the lesion. This observation is in line with the significant correlation of intramedullary localization and occurrence of irreversible postoperative deficit in patients with spine lesions in the retrospective study. Furthermore, the limited duration of this study did not allow scoring of long term (3 months) postoperative outcome. It is possible that several patients have improved from short term postoperative deterioration.

There is a scarcity of published data on neurologic outcome after IONM-assisted neurosurgical procedures in patients with (peri-)rolandic brain, CPA and spine lesions. Furthermore, outcome rates and definitions of neurologic deterioration vary among authors (61-63). We consider the rates of irreversible neurologic deterioration reported in our retrospective study as a reference for future studies at ZOL.

5. Conclusion and future research

From this study can be concluded that IONM does not exclude the risk of irreversible postoperative deterioration in (peri-)rolandic brain, CPA and spine surgery. However, postoperative deterioration does not by definition mean complete contralateral hemiparesis, complete facial nerve palsy or complete paraparesis. No significant correlation between IONM parameter changes and neurologic deterioration were found. However, the postoperative clinical scores show a good outcome in treatment naïve patients without preoperative neurologic deficits. Insights of the prospective observational pilot study will be used in a large-scale prospective study to obtain sound and reliable electrophysiological-clinical correlations, considering factors influencing IONM parameters (lesion histology, duration of anesthesia, total anesthetic doses, systolic blood pressure, body temperature) as well as factors influencing long-term outcome (age, reoperation after tumor recurrence and pre-existing deficits). To enable statistical significant correlations, high variability in the patient groups is necessary. Specific histologic diagnoses (gliomas in (peri-)rolandic brain lesions, vestibular schwannomas in CPA lesions, ependymomas in intramedullary spinal cord tumors) must be studied in large cohorts to avoid heterogenic and small sized subgroups. Correlations generated from this large-scale study will enable the establishment of center-specific warning criteria for postoperative deterioration to further reduce the risk of irreversible neurologic deterioration in (peri-)rolandic brain, CPA and spinal cord tumor surgery at ZOL, by optimal use of multimodal IONM. In a next stage, the documentation on postoperative outcome in IONM-assisted neurosurgery will be of value to argue for recognition and reimbursement of IONM by the Belgian Ministry of Health.

6. References

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7. Supplemental data

Table S1: Preoperative and postoperative strength of the upper and lower limb muscles in the (peri-)rolandic brain lesion patients.

Muscle	Deltoid		Biceps		Triceps		Wrist flex		Wrist ext		Hand		Iliopsoas		Quadriceps		Hamstrings		Ankle flex		Ankle ext	
PR	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
#5	5-	5-	5	5	5-	5-	5-	5-	5	5	5-	5-	5	5	5	5	5	5	5	5	5	5
#6	4	4	4	4	4+	4+	4+	4+	4	4	4	4	4	4	4	4	4+	4+	4+	4+	4	4+
#8	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
#9	5	5	4+	4+	5	5	5	5	5	5	5	5	4+	4+	5	5	5	5	5	5	5	5
#10	1	0	1	0	1	0	1	0	1	0	1	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
#13	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
#14	5-	0	5-	0	5-	0	4+	0	4+	0	4+	0	5	3	5	4	5	1	5	4	5	4
#18	0	0	1	1	2	2	0	0	0	0	2	2	5	3	5	3	4	3	5	4	5	4
#21	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
#23	3	3	3	3	2	2	4	3	3	3	3	3	2	2	2	2	2	2	3	3	3	2
#24	3	4+	4	4+	4	5-	3	4	3	4+	3	3	4	4	5	5	4+	5-	5	5	5	5-
#26	3	+2	4	4	4	4	3	2	3	3	3	3	1	1	3	1	1	1	1	1	1	1
#28	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
#29	5	5	5	5	5	5	5	5	5	5	5	5	5	5-	5	5	5	5	5	5	5	5
#32	5	5	5	5-	5	5-	5	4+	5	4	5	3	4+	5	5	5	5	5	5	5	5	5

Muscle strength is scored according to the modified Medical Research Council (MRC) scale; 0: complete paralysis; 1: minimal contraction; 2: active movement with gravity eliminated; 2+: brief active movement against gravity*; 3-: sustained active movement against gravity*; 3: active movement against gravity**; 3+: brief active movement against slight resistance*; 4-: sustained active movement against slight resistance*; 4: active movement against slight resistance**; 4+: movement against strong resistance*; 5-: movement against strong resistance; 5: normal strength; *<50%, **>50% range of joint movement; PR, procedure.

Table S2: Preoperative and postoperative cranial nerve palsy in the CPA lesion patients.

	n. III		n. IV		n. V		n. VI		n. VII		n. IX		n. X		n. XI	
PR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
#1			3	3	3	3			3	3	3	3				
#2					3	3	3	3	3	3	3	3				
#3					3	3			3	3	3	3			3	3
#4									3	3						
#7			3	3	3	3	3	3	0	0	3	3				
#12									3	0						
#16					3	3			3	3	3	3				
#17					3	3			3	3						
#19	3	3	3	3	3	3	0	0								
#27					3	3			3	3						

Cranial nerve palsy is scored according to a scale analogous to the simplified Medical Research Council (sMRC) scale; 0: complete deficit; 1: severe deficit; 2: slight deficit; 3: normal function; PR, procedure.

Table S3: Preoperative and postoperative strength of the right and left upper and lower limb muscles in the spine lesion patients.

Muscles	(R, L)\PR	#15	#20	#22	#25	#30	#31	#33	#34
Deltoid	Pre							5,5	
	Post							3,3	
Biceps	Pre							5,5	
	Post							3,3	
Triceps	Pre							5,5	4,2
	Post							4,4	1,0
Wrist flex	Pre							5,5	
	Post							3,3	
Wrist ext	Pre							5,5	5-,2+
	Post							3,3	3,0
Hand	Pre							5,4+	
	Post							3,3	
Iliopsoas	Pre	0,0	4,4+	5,5	5,5	5,5	3+,2	5,5	3,1
	Post	2,2	4+,4+	4,5-	5,5	5,5	2,0	3,3	1,0
Quadriceps	Pre	2+,3	5,5	5,5	5,5	5,5	5,4+	5,5	4,3
	Post	4,4	5,5	5,5	5,5	5,5	5,4	5,4	3,0
Hamstrings	Pre	0,0	4,4+	5,5	5,5	5,5	5,4	5,5	4,2
	Post	3,2	4,4+	5,5	5,5	5,5	4,1	3,3	1,0
Ankle flex	Pre	0,0	4,5-	5,5	5,5	5,5	5,4+	5,5	5,4
	Post	2,2	2,5-	5,5	5,5	5,5	5,4	4,4	1,0
Ankle ext	Pre	0,0	3,5-	5,5	5,5	5,5	5,3	5,5	5-,2+
	Post	4,4	3,5-	5,5	5,5	5,5	5,2	4,3	3,0

Muscle strength is scored according to the modified Medical Research Council (MRC) scale; 0: complete paralysis; 1: minimal contraction; 2: active movement with gravity eliminated; 2+: brief active movement against gravity*; 3-: sustained active movement against gravity*; 3: active movement against gravity**; 3+: brief active movement against slight resistance*; 4-: sustained active movement against slight resistance*; 4: active movement against slight resistance**; 4+: movement against strong resistance*; 5-: movement against strong resistance; 5: normal strength; *<50%, **>50% range of joint movement; PR, procedure; R, right; L, left.

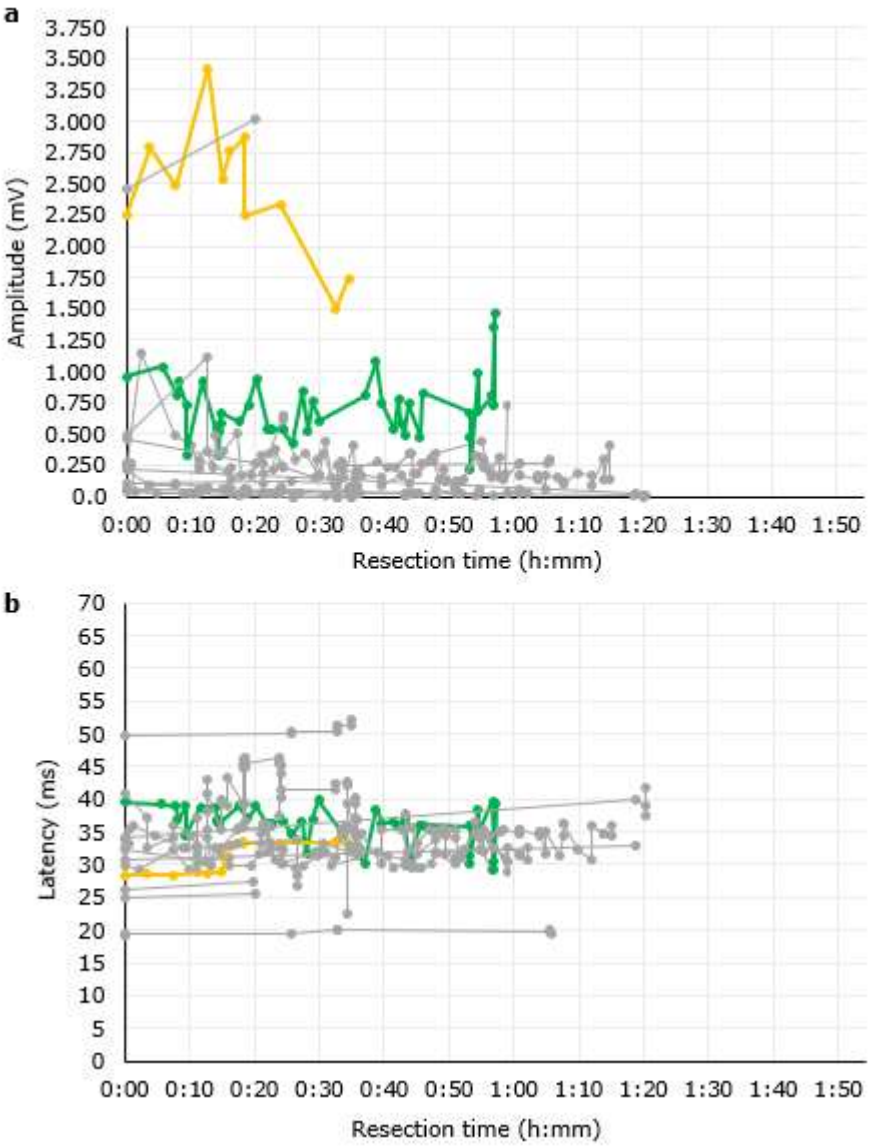

Figure S1: Course of absolute tMEP amplitude and latency recorded in the tibialis anterior muscle during resection of spinal lesions. Data are from six spine lesion patients with successful tMEPs in the left and right tibialis anterior muscle; Case 3 is presented in yellow; Case 4 is presented in green; tMEP monitoring was initiated at the start of lesion resection and finalized after removal of the lesion; **a:** The absolute amplitude (millivolts) of tMEPs in the tibialis anterior muscle shows a high trial-to-trial variability within and between case 3 and 4. An incremental effect can be observed in both cases after multiple consecutive stimuli within seconds; **b:** The absolute latency (miliseconds) of tMEPs in the tibialis anterior muscle of both cases shows a very low intra- and interpatient trial-to-trial variability and no incremental effect after multiple consecutive stimuli.

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Datum: **11/06/2018**