Intraoperative neurophysiological mapping and monitoring in spinal tumor surgery: sirens or indispensable tools?

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Spinal tumor (ST) surgery carries the risk of new neurological deficits in the postoperative period. Intraoperative neurophysiological monitoring and mapping (IONM) represents an effective method of identifying and monitoring in real time the functional integrity of both the spinal cord (SC) and the nerve roots (NRs). Despite consensus favoring the use of IONM in ST surgery, in this era of evidence-based medicine, there is still a need to demonstrate the effective role of IONM in ST surgery in achieving an oncological cure, optimizing patient safety, and considering medicolegal aspects. Thus, neurosurgeons are asked to establish which techniques are considered indispensable. In the present study, the authors focused on the rationale for and the accuracy (sensitivity, specificity, and positive and negative predictive values) of IONM in ST surgery in light of more recent evidence in the literature, with specific emphasis on the role of IONM in reducing the incidence of postoperative neurological deficits. This review confirms the role of IONM as a useful tool in the workup for ST surgery. Individual monitoring and mapping techniques are clearly not sufficient to account for the complex function of the SC and NRs. Conversely, multimodal IONM is highly sensitive and specific for anticipating neurological injury during ST surgery and represents an important tool for preserving neuronal structures and achieving an optimal postoperative functional outcome.

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KEY WORDS D wave; electromyography; intraoperative monitoring; motor evoked potential; spinal tumor surgery; somatosensory evoked potential

Despite recent advances in the neurosurgical strategies adopted for the treatment of spinal tumors (STs), the surgery still bears the significant risk of causing intraoperative damage, with morbidity ranging from 3.7% to 7.5%. The neurosurgical goal is to achieve a maximal safe resection, a compromise between the best oncological result and the preservation of neurological function. For this, intraoperative neurophysiological monitoring and mapping (IONM) represents the most effective technique for identifying and monitoring in real time the functional integrity of both the spinal cord (SC) and the nerve roots (NRs). And although there is increasing evidence and consensus among experts that IONM is valuable in spine surgery and level A recommendations have been published regarding the fact that surgeons and other members of the operating team should be alerted to the increased risk of severe adverse neurological outcomes in patients with significant IONM changes, no studies in humans have directly measured the efficacy of operative and/or anesthetic interventions in these cases. Moreover, to prevent rather than merely predict the occurrence of a postoperative neurological injury, the team needs a long educational period with expert-based training to be able to discriminate between alerts (false positive and false negative); a specifically IONM-oriented operating theater setup; and mutual collaboration in wiring, screwing, tapping, monitoring, vein and artery cannulating, cuffing, and even positioning the patients and the IONM tools.

ABBREVIATIONS BCR = bulbocavernosus reflex; CST = corticospinal tract; D wave = direct wave; DCM = dorsal column mapping; DNS = direct nerve stimulation; EXDST = extradural spinal tumor; fEMG = free-running electromyography; IDEMSCT = intradural-extramedullary SC tumor; IMSCT = intramedullary spinal cord tumor; IONM = intraoperative neurophysiological monitoring and mapping; MEP = motor evoked potential; mIONM = multimodal IONM; mMEP = muscle MEP; NPV = negative predictive value; NR = nerve root; PPV = positive predictive value; SC = spinal cord; SSEP = somatosensory evoked potential; ST = spinal tumor.

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In this era of evidence-based medicine, there is still a need to demonstrate the effective role of IONM in ST surgery to improve patient safety and outcomes and to reduce malpractice issues. We are asked to prove that monitoring “really makes a difference” and to establish which tools are sirens and which are indispensable tools. Our aim in this study was to address the rationale for and the accuracy (in terms of sensitivity and specificity, positive and negative predictive value) of IONM in light of more recent evidence in the literature, with specific emphasis on evaluating the role of IONM in reducing the incidence of postoperative neurological injury and mitigating its severity.

Methods

We performed a literature search of the Medline, Embase, and Ovid (latest access March 30, 2016) databases using the key words “intraoperative,” “monitoring,” and “spinal tumor,” highlighting papers addressing the accuracy and validation of individual IONM techniques, each technique’s prognostic significance, and its role as a single tool and in a multimodal integrated setup. We focused on papers dealing with STs. In the literature, 2 main strategies for IONM during spinal surgery have been described for assisting in the diagnosis of neurological injury. Basically, the monitoring techniques allow for functional assessment of neuronal integrity and the mitigation of injury severity, while mapping serves to identify the anatomical and functional locations of the SC and NRs. To make appropriate selections from among the identified papers, we considered a minimum cohort size to be 10 patients for the inclusion of articles dealing with monitoring techniques; however, no limitations on cohort size were used as a criterion for including articles dealing exclusively with mapping procedures because of the limited number of pertinent studies. Exclusion criteria were non-English language articles, articles dealing with IONM of diseases other than STs, and series published in the pre-microneurosurgical era. Records were identified and independently reviewed by 2 physicians (A.S. and G.R.). Additional articles found among the cited references in the reviewed studies were included as well.

Results

The literature search identified an initial set of 274 reports. Figure 1 features a flow diagram of the selection process for identifying studies for review. We excluded 187 records because they did not cover the topic of this study or they were nonclinical studies. The full text of the remaining 87 articles was reviewed, and 33 met our selection criteria. Fifty-four papers were excluded because they were written in a language other than English (14 articles), they were focused on other spinal pathologies (15 papers), or their study cohort was smaller than 10 patients (25 papers). Six additional articles covering the study topic and meeting our inclusion criteria were found among the references of initially selected articles and thus were included.
Intraoperative neurophysiological monitoring spinal tumor surgery

**TABLE 1. Literature review of mMEP warning criteria focused on ST surgery**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Pathology</th>
<th>No. of Patients</th>
<th>mMEP Warning Criteria</th>
<th>Other IONM</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Köthbauer et al., 1998</td>
<td>IMSCT</td>
<td>100</td>
<td>Presence/absence of response</td>
<td>SSEP, D wave</td>
<td>100%</td>
<td>91%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Quiñones-Hinojosa et al., 2005</td>
<td>IMSCT</td>
<td>28</td>
<td>Alterations in morphology &amp; reduction in duration</td>
<td>SSEP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sala et al., 2006</td>
<td>IMSCT</td>
<td>100 (50 w/ IONM + 50 historical controls)</td>
<td>Presence/absence of response</td>
<td>SSEP, D wave</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Krammer et al., 2009</td>
<td>ST</td>
<td>31</td>
<td>Amplitude decrease 50%, latency increase 10%, threshold increase 20%</td>
<td>SSEP</td>
<td>NA</td>
<td>83%</td>
<td>86%</td>
<td>63%</td>
</tr>
<tr>
<td>Hyun &amp; Rhim, 2009</td>
<td>IMSCT</td>
<td>17</td>
<td>Amplitude decrease 50%</td>
<td>SSEP</td>
<td>100%</td>
<td>25%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Forster et al., 2012</td>
<td>ST</td>
<td>203</td>
<td>Presence/absence of response</td>
<td>SSEP, D wave</td>
<td>95%</td>
<td>98.9%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kobayashi et al., 2014</td>
<td>ST, orthopedic</td>
<td>959 (360 ST)</td>
<td>Amplitude decrease 70% or more</td>
<td>NA</td>
<td>95%</td>
<td>91%</td>
<td>33%</td>
<td>99%</td>
</tr>
<tr>
<td>Choi et al., 2014</td>
<td>IMSCT</td>
<td>50</td>
<td>Amplitude decrease 75%</td>
<td>SSEP</td>
<td>94%</td>
<td>94%</td>
<td>89%</td>
<td>97%</td>
</tr>
</tbody>
</table>

NA = not available.
* The PPV and NPV refer to all patients, not only those with STs.

Data were obtained from 28 papers that dealt with monitoring and 11 articles that dealt with mapping techniques.

**Monitoring Techniques**

**Somatosensory Evoked Potentials**

Somatosensory evoked potentials (SSEPs) provide monitoring of the dorsal column and medial lemniscus pathways that carry tactile discrimination, vibration, and joint and/or muscle sensation through stimulation of the median nerve at the wrist, the posterior tibial nerve at the ankle, and the pudendal nerve (intensity 40 mA, duration 0.2 msec, repetition rate 4.3 Hz) and through recording by corkscrew-like electrodes inserted in the scalp at Cz/Fz (legs) and C3/C4/Fz (arms), according to the International 10-20 system of electrode placement. Transcranial electrical stimulation with a multipulse technique is used for eliciting mMEPs and includes short trains of 5 square-wave stimuli (single pulse duration 0.5 msec, interstimulus interval 4 msec, rate 2 Hz) through corkscrew electrodes placed at C1/C2 (lower limbs) and C3/C4 (upper limbs) scalp sites. The mMEPs are recorded through needle electrodes inserted into the upper- and lower-extremity muscles; they do not require averaging, but they do have wide amplitude and morphological variability. In monitoring conus medullaris and cauda equina motor integrity during ST surgery, mMEPs are the most reliable method. Different warning criteria for mMEPs during ST surgery have been proposed: presence or absence of responses, changes in thresholds, changes in waveform, or amplitude variations with the first listed criterion being the most effective. In ST surgery, mMEP sensitivity in anticipating postoperative motor deficits ranges from 75% to 100%, with a specificity from 25% to 100%, a positive predictive value (PPV) ranging from 63% to 100%, and a negative predictive value (NPV) ranging from 75% to 97% (Table 1).

In conus medullaris and cauda equina tumor surgery, it is imperative to maintain and preserve MEPs; any loss may indicate a complete lower motor neuron lesion, anticipating a postoperative motor deficit with little tendency to recover. In case of an alert, surgeons should pause the procedure and irrigate with warm saline solution and papaverine while the anesthesiologist increases blood pressure.

**Direct Wave: A Single-Pulse Technique.**

The direct (D) wave is a direct measure of the number of functioning fast-conducting fibers in the corticospinal tract (CST). As fibers numerically decrease cranio-caudally and are absent in the lumbar-sacral region, the use of D waves is limited in the cord up to T10–11. The D wave is elicited by a single-pulse stimulating technique (0.5 msec duration) and are recorded from the epidural or subdural spaces of the SC. In contrast to mMEPs and SSEPs, the D wave is not influenced by blood pressure, heart rate,

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temperature, and anesthesia drugs, but it needs midline recording. A warning criterion is a decrease of more than 50% of the baseline amplitude. Although D-wave monitoring is actually considered the gold standard for assessing the integrity of the CST in spinal monitoring, no study in the literature has specifically addressed the issue of D-wave accuracy in ST surgery.

Free-Running (Spontaneous) Electromyography

Free-running electromyography (frEMG) intraoperatively monitors NRs, with spontaneous activity recorded via needle electrodes placed in the muscles of interest. Relevant frEMG activity includes spikes, bursts, or trains, and the occurrence of neurotonic discharges during IONM may anticipate nerve injury. In the literature, only the report by Skinner et al. specifically addresses the role of frEMG in detecting early motor tract injury during ST surgery. Warning criteria were 1) irregular aperiodic bursts repeatedly elicited by surgical maneuvers within the tumor bed; 2) prolonged (> 3 sec), focal, semi-rhythmic tonic discharges; and 3) an acute drop in signal in one or more limbs. Free-running EMG sensitivity and specificity were 87.5% and 83.3%, respectively; its PPV was 87.5% and NPV was 83.3%.

Bulbocavernous Reflex

The bulbocavernous reflex (BCR) is the most useful intraoperative tool for monitoring sphincter function in real time. The dorsal penile or clitoral nerves are stimulated with 2 surface electrodes, and recordings are obtained from the external anal sphincter muscle via wire or needle electrodes. To elicit the BCR, a short train of 5 stimuli is used. No alert criteria exist for the intraoperative BCR, with the disappearance of the response considered an alarm, especially when occurring in surgery with a consistent risk of postoperative sphincter dysfunction. However, intraoperative BCR data and their correlation with long-term sphincter control, sphincter-detrusor dysfunction, and sexual function, especially in ST surgery, need further investigation.

Mapping Techniques

Dorsal Column Mapping

Dorsal column mapping (DCM), a tool described in a limited number of reports, is a useful technique for intraoperative midline localization during posterior myelotomy, to avoid the “dorsal column dysfunction” syndrome (numbness, painful dysesthesias below the surgical level, proprioceptive loss, and gait dysfunction). Three main techniques have been described: 1) In 2002, Quiñones-Hinojosa et al. described 2 patients in whom antidromically elicited SSEPs were evoked by stimulation of the dorsal column and were recorded with subdermal electrodes placed at the medial malleolus bilaterally. 2) In 2010, in a group of 10 patients with intramedullary spinal cord tumor (IMSCT), Yanni et al. described the registration of SSEPs from a miniature microelectrode grid (made up of 8 parallel Teflon-coated stainless steel wires) placed over the posterior SC surface after stimulation of both tibial nerves at the ankle (stimulus intensity 40 mA, duration 0.2 msec, rate 13.3 Hz). 3) In 2012, Simon et al. published a case report describing the use of the “gracilis tract SSEPs phase-reversal technique” consisting of SSEP recording through scalp electrodes after direct electrical stimulation using an 8-contact mini-electrode strip placed on the dorsal SC. In 2012, Mehta et al. described the use of DCM during surgery in 11 patients with IMSCT, comparing their outcomes with those of a control group of 80 patients. These authors found a decreased rate of postoperative posterior column dysfunction using intraoperative DCM.

Intramedullary Motor Mapping

A few reports in the literature focus on techniques useful for real-time identification of the anatomical site of the CST within the SC, Dufox et al. in 1998, described the use of a modified bipolar probe (4 mm distance of stimulating surfaces) for direct medullary electrical stimulations (60 Hz, biphasic square-wave pulses with 1 msec/phase, 0.9 mA) during surgery in 3 patients with IMSCT. These authors concluded that direct medullary electrical stimulation is a safe, easy, precise, and reliable method of reducing morbidity during SC surgery. In 2001, Deletis et al. described the “D-wave collision technique,” obtained by simultaneous stimulation of the SC and transcranial electrical stimulation. As the resulting signals are transmitted along the same axons, the descending D wave collides with the ascending signal carried antidromically along the CST. It results in a decrease in the D-wave amplitude caudally to the collision site. Even in the early stages of its development, this methodology has proven to be highly successful in identifying and localizing the CST within the SC. In 2002, Quiñones-Hinojosa et al. described the resection of 2 IMSCTs using the Ojemann cortical stimulator (model OCS-1 with stimulating tips 5 mm apart). Stimulation of abnormal tissue within the tumor did not elicit electromyographic activity. These authors concluded that mapping SC motor tracts with direct SC stimulation and electromyographic recording facilitated a more extensive resection. In 2015, Gandhi et al. described the use of intraoperative motor fiber tract stimulation to map the CST associated with a cervicomedullary junction cystic ependymoma. High-resolution motor mapping was performed using a Kartush concentric bipolar stimulating probe (overall width of 2 mm) with a biphasic waveform (repetition rate 60.11 Hz, pulse width 1.0 msec, stimulation intensities ranging from 0.1 to 1.0 mA) with registrations on individual muscle groups. They stated that high-resolution mapping of the SC motor pathways by using direct fiber stimulation may improve the safety of IMSCT surgery.

Triggered EMG: Direct Nerve Stimulation

Intraoperative identification of motor NRs is accomplished by direct electrical handheld monopolar or bipolar forceps stimulation. Recording from the target muscles reveals the EMG responses supplied by the stimulated NR. In the literature, a limited number of reports describe the intraoperative use of direct nerve stimulation (DNS). In 2006, Guo et al. described triggered EMG during surgery in 10 intraspinal cervical dumbbell and foraminal tumors; DNS and recording of compound muscle
action potentials facilitated NR identification, anticipating the postoperative function. These authors concluded that DNS may also be useful in predicting postoperative outcome when NR sacrifice is necessary, despite the absence of an intraoperative motor response. Similar conclusions were provided by Kaneko et al. in 2006, in their series of 5 cervical schwannomas.

**Multimodal IONM**

The accuracy of IONM is increased when multiple tools are simultaneously employed. Few studies have specifically addressed the value of multimodal IONM (mIONM) in ST surgery (Table 2). In 2007, Sutter et al. published a prospective series of 109 patients demonstrating a sensitivity and specificity of 92% and 99%, respectively, with a PPV of 96% and NPV of 98%. These authors concluded that mIONM is an effective method of monitoring SC and NR function in ST surgery and can reduce or even prevent the occurrence of postoperative neurological deficit. In 2010, Malhotra and Shaffrey, in a large retrospective systematic review of 187 publications, concluded that mIONM may be useful in preserving neurological function where modifications of the surgical approach are possible. In 2009, Hyun and Rhim described the combined use of mMEPs and SSEPs during surgery on 17 IMSCTs. They reported a sensitivity of 100% and a specificity of 83%, concluding that combined SSEP and mMEP monitoring provided higher sensitivity and higher PPV and NPV than a single-modality technique. In 2015, Korn et al. assessed the use of mIONM during surgery on 100 patients with intradural-extradural SC tumors (IDEMSCSTs). In their series, mIONM demonstrated a sensitivity, specificity, PPV, and NPV of 82%, 95%, 82%, and 95%, respectively, allowing the authors to conclude that mIONM is useful in the context of IDEMSCTs for identifying iatrogenic injury to the SC.

**Discussion**

Spinal tumor surgery carries the risk of new neurological deficits in the postoperative period. Despite consensus in the neurosurgical community favoring the use of IONM in ST surgery, there is still a need for a definite strategy to routinely and safely monitor the SC and NRs intraoperatively, assisting in diagnosis and anticipating the occurrence of postoperative neurological injury.1

In the present study we addressed the rationale for and the accuracy (in terms of sensitivity, specificity, PPV, and NPV) of IONM in ST surgery in light of more recent evidence in the pertinent literature. Although there are numerous validated techniques that can map and monitor different SC and NR functions, each method alone cannot significantly reduce the incidence of neurological injury or mitigate its severity. Conversely, the accuracy of IONM is increased when multiple tools are simultaneously employed, reaching a sensitivity, specificity, PPV, and NPV as high as 100%, 99%, 96%, and 100%, respectively. Although few studies have specifically addressed the value of mIONM in ST surgery, the results are important for an oncological cure while ensuring patient safety and considering medicolegal aspects.
The first regular attempt to intraoperatively check for SC and NR function was made in the 1970s by introducing the “wake up” test. Although the use of this test decreased the incidence of postoperative neurological deficits, it did not allow for the continuous monitoring of SC and NR function. Nowadays, despite the wide use of IONM in complex spinal surgeries, there is still ongoing debate on what is considered an indispensable tool. In 2012, Nuwer et al., on behalf of the American Academy of Neurology, evaluated 40 studies dealing with IONM during spine surgery. They restricted their analysis to 4 Class I and 8 Class II studies with an evidence-based approach, providing evidence that persistent changes in IONM correlated with the occurrence of new neurological deficits in the postoperative period. The authors concluded that IONM is effective in predicting an increased risk of postoperative neurological deficits and that the specialists and other participants of an operative team should be notified about the increased risk of adverse neurological events in patients with significant IONM changes (level A). In 2010, similar results were described by Fehlings et al. in a systematic review of 103 papers; they found a high level of evidence that mIONM is accurate for anticipating neurological sequelae in spine surgery, a low level of evidence that mIONM decreases the occurrence of new or worsened perioperative neurological deficits, and a very low level of evidence that an intraoperative response to neuromonitoring warnings reduces the rate of perioperative neurological deterioration. In their conclusions, the authors recommended the use of mIONM in spine surgery in which the SC or NRs are deemed to be at risk. In 2006, Sala et al. quantified the real impact of mIONM (SSEP, mMEP, and D wave) in intramedullary ST surgery by comparing the neurological outcome of 50 patients with those of a historical control group of equal size. The authors reported that the level of evidence for the use of IONM in IMSCT surgery remained confined to Class II and III studies as a prospective randomized study was unacceptable for ethical and medicolegal reasons. They concluded that a combined mMEP and D-wave protocol significantly improved motor outcome at 3 months. While different studies in the literature highlighted the value of IONM during IMSCT surgery (Table 2), its routine use during IDEMSCT and extradural ST (EXDST) surgery is still under debate. Among the studies specifically addressing the outcome of patients undergoing surgery for IDEMSCT with IONM, Ghadirpour et al., in 2015, described a series of 68 patients who underwent mIONM (SSEP, mMEP, and D wave); significant IONM changes occurred in 7.35% of patients, inducing a modification of the surgical strategy that was able to prevent and mitigate postoperative neurological sequelae. As IONM predicted a good neurological outcome in 92.65% of their patients, these authors concluded that IONM allowed for safer tumor removal. Also in 2015, Korn et al., examined IONM results in 100 patients with IDEMSCT. Multimodal IONM demonstrated a high level of accuracy, with sensitivity and specificity as high as 82% and 95%, respectively, PPV of 82%, and NPV of 95%. These authors concluded that IONM is feasible and useful in the treatment of IDEMSCTs, particularly in identifying injury to the SC. Conversely, in a series of 131 spinal meningiomas operated on with SSEPs, Sandalcioglu et al. reported an improved or unchanged neurological status in 96.2% of patients and a worsened status in 3%; the authors concluded that good clinical outcomes could be reached without the use of sophisticated monitoring. In a different ST scenario, that is, EXDSTs, the utility of IONM was the focus of Avila et al. in 2013. They evaluated 152 patients undergoing decompression for EXDST compression with mIONM (SSEP, mMEP, and EMG), concluding that this combination increased the accuracy of monitoring and was important given the risk of SC injury due to instrumentation and resection of tumor causing SC compression.

Different inferences should be made regarding mapping techniques. Mapping of neural structures during ST surgery could be considered a well-established method for spinal NR lesions. On the other hand, mapping techniques of motor and sensory functions of the SC are a relatively new application; therefore, the number of patients evaluated is still limited. Nevertheless, although it is difficult to draw definitive conclusions, current data suggest that these techniques may be useful tools to minimize postoperative motor and sensory dysfunction.

Conclusions

This review confirms the role of mIONM as an essential tool in the operative workup for ST surgery. Single monitoring procedures are clearly not sufficient to account for the complex function of the SC and NRs. On the other hand, mIONM is highly sensitive and specific for anticipating neurological injury during ST surgery and represents an important tool in preserving neuronal structures and achieving an optimal postoperative functional outcome.

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Author Contributions
Conception and design: all authors. Acquisition of data: Scibilia, Terranova, Morelli, Esposito. Analysis and interpretation of data: Raffa, Scibilia, Esposito, Germanò. Drafting the article: Raffa, Scibilia, Esposito. Critically revising the article: Raffa, Scibilia, Terranova, Esposito, Conti, Quararone, Germanò. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Raffa. Statistical analysis: Raffa. Administrative/technical/material support: Mallamace. Study supervision: Raffa, Scibilia, Terranova, Conti, Quararone, Germanò.

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