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Multimodal intraoperative neurophysiological monitoring may better predict postoperative distal upper extremities' complex-functional outcome than spinal and muscular motor evoked potentials alone in high-cervical intramedullary spinal cord tumor surgery

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ABSTRACT

Objective: D-wave can safely monitor the corticospinal-tract (CST)-function regarding gross-motor outcome of lower extremities, but it is still unknown whether i)D-wave can also safely monitor the gross-motor outcome of distal upper extremities in those patients undergoing high-cervical intramedullary-spinal-cord-tumor (IMSCT)-resection (enabling epidural D-wave-placement below C5) and ii)multimodal IONM can also predict fine-motor/complex hand function.

Methods: We prospectively assessed 20 patients undergoing IMSCT-surgery above the C4/5-level with multimodal IONM (D-wave/mMEPs/EMG/SSEPs). Detailed gross-/fine-motor and complex hand function was assessed pre- and postoperatively and during long-term follow-up (mean:29.5 ± 18.8 months) and correlated with IONM-findings.

Results: D-wave monitoring was without intraoperative critical changes in all patients and none had any permanent postoperative gross-motor deficits. However, D-wave did not allow to predict the occurrence of mild permanent postoperative deficits affecting fine-motor function which was the case in 8% for distal upper extremities. The complex distal upper extremities' function assessed by Nine-Hole-Peg-Test (reflecting the complex motor/sensory interaction for hand-usability) was permanently deteriorated in 15% postoperatively and only the combination of D-wave/mMEPs/EMG/SSEPs was able to provide a viable predictive power (specificity:79%/sensitivity:43%).

Conclusions: In high-cervical IMSCT-surgery, unimpaired D-wave reliably predicts preserved gross-motor function, but fails to sufficiently cover distal upper extremities' fine-motor/complex function.

Significance: Our study underlines the importance of multimodal IONM for fine-motor/complex hand function.

1. Introduction

Approximately 40 years ago, somatosensory evoked potentials (SSEPs) were first used to monitor spinal cord integrity during surgical correction for scoliosis [Nash et al, 1977; Engler et al, 1978]. Despite early enthusiasm, the presence of serious motor deficits despite preserved SSEPs in several cases led to a questioning of their capability to monitor the spinal cord motor tracts [Lesser et al, 1986]. The introduction of transcranially motor evoked potentials (TcMEPs), however, represented a significant step forward for intraoperative assessment of

Abbreviations: BI, Barthel Index; ca, circa; CST, corticospinal tract; DCM, dorsal column mapping; D wave, direct wave; FN, false-negative; FP, false-positive; frEMG, free-running elctromyography; i.a, inter alia; IMSCT, intramedullary spinal cord tumor; IONM, intraoperative neurophysiological monitoring; KPS, Karnofsky Performance Scale; mJOA, modified Japanese orthopaedic association score; MRC, Medical Research Council; MRI, magnetic resonance imaging; mTcMEPs, muscular transcranially motor evoked potentials; NHPT, Nine-Hole Peg Test; NPV, negative predictive value; PPV, positive predictive value; PSA, persistent/pathological spontaneous activity; PSS, Performance Status Scale; resp., respectively; SD, standard deviation; SF-36, Short Form (SF)-36v2® Health Survey; SSEPs, somatosensory evoked potentials; TcMEPs, transcranially motor evoked potentials; USA, United States of America; WHO, World Health Organization.

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motor pathway function during spinal cord surgery [Boyd et al, 1986; Hicks et al, 1991; Burke et al, 1992; Pechstein et al, 1996; Jones et al, 1996; Kothbauer et al, 1998; Deletis and Sala, 2008a]. Two distinct modalities have been developed to elicit TcMEPs [Deletis and Sala, 2008a]: 1) recording the direct wave (D wave) directly from the epidural or subdural space with a single pulse technique [Boyd et al, 1986; Hicks et al, 1991] or 2) recording of MEPs in limb muscles with a multipulse technique (mTcMEPs) [Pechstein et al, 1996; Jones et al, 1996].

While mTcMEPs also depend on the excitability of facilitatory cortical motoneurons beyond the spinal cord conductivity and the excitability of lower motoneurons [Deletis and Sala, 2008a,b], D wave is generated by the direct activation of the fast-conducting fibers of the corticospinal tract (CST) [Patton and Amassian, 1954] and have, therefore, nonsynaptic, linear, and stable properties with hardly any influence by blood pressure, heart rate, temperature, and anesthesia drugs [Costa et al, 2013]. Therefore, D wave is considered to be the gold standard for assessing the functional integrity of CST caudally to the level of its placement and there is a strong evidence in literature for a 50 % amplitude reduction criteria during intramedullary spinal cord tumor surgery (IMSCT) in terms of postoperative occurrence/absence of permanent severe paraparesis/paraplegia [Kothbauer et al, 1998; Deletis and Sala, 2008a; Costa et al, 2013; Sala et al, 2007; MacDonald, 2017; Sala et al, 2006; Kothbauer et al, 1997; Verla et al, 2016; Scibilia et al, 2016; Park and Hyun, 2015]. However, none of these studies so far have specifically addressed the predictive value of D wave monitoring for the detailed neurological as well as fine-motor and functional outcome of the lower extremities exceeding the graduation into coarse compound scores (e.g. McCormick scale) or the mere dichotomization in ambulatory or not. More importantly, no study in literature has so far evaluated if D wave monitoring can also safely monitor the integrity of the CST with regard to distal upper extremities' motor function in cases where D wave has been placed in the upper cervical spinal cord and should therefore cover the integrity of those CST fibers conveying the corresponding information for the upper extremities, or at least the forearm and hand-muscles.

Our prospective study is therefore the first to elucidate if D wave can safely monitor the CST during high-cervical IMSCT surgery and if it can reliably predict both the gross-motor outcome as well as the detailed fine-motor and complex-functional outcome of both the lower and also the distal upper extremities in terms of multimodal IONM with mTcMEPs, SSEPs and free-running EMG (frEMG) in the short- and long-term follow-up.

2. Methods

All patients had been referred to our institute (Department of Neurosurgery, Ludwig-Maximilians-University Hospital, Munich, Germany) from April 2017 to April 2023 for multimodal IONM-aided microsurgical resection of an IMSCT in the cervicothoracic spine. To truly assess whether D wave can safely monitor the CST fibers conveying motor signals for both upper and lower extremities, only patients with IMSCT above the C4/5-level were included allowing intraoperative D wave placement caudally to the surgical level to safely cover the segment of C5 and the lower cervical segments at least with the most rostrally located D wave electrode. After study approval by the local Institutional Review Board (AZ17-145), these patients were prospectively enrolled following informed consent. We collected and analyzed epidemiological aspects, clinical characteristics, imaging findings, management strategies, operative and IONM records, complications, and detailed individual short- and long-term outcomes.

2.1. Neurological and clinical evaluation

Detailed neurological assessment (including sensory, reflex, muscle tonus and gait examinations) and fine-motor evaluation via the Medical Research Council (MRC) grading system for muscle strength [Compston et al, 2010] as well as complex-functional evaluation via hand-force manometer (reference value: within the range of ± 2SD from the sex- and age-related population's normal value; changes > 2SD from preoperative baseline were considered as clinically significant) and Nine-Hole Peg Test (NHPT; reference value: dominant hand < 19 sec.; non-dominant hand < 21 sec.; changes > 20 % from preoperative baseline were considered as clinically significant) [Kellor et al, 1971; Mathiowetz et al, 1985; Oxford Grice et al, 2003] was performed in all patients before and after surgery as well as at the 3- and 6-months and last follow-up timepoint. For assessment of specific spinal cord segment deficit, reference muscles were defined to be trapezius and supra-/infraspinatus muscle for C4, deltoid muscle for C5, biceps and brachioradialis muscle for C6, triceps muscle and wrist extensor muscles for C7, hypothenar muscles for C8, and interosseous muscles for C8 and Th1. Postoperatively new or worsened sensorimotor deficits and bladder/bowel dysfunction as well as pain or painful dysaesthesia were recorded.

The classification of McCormick [McCormick et al, 1990] and the modified Japanese orthopaedic association score (mJOA) [Benzel et al, 1991] were used for gross-functional evaluation, while the Short Form (SF)-36v2® Health Survey [Ware et al, 2007] and the Barthel Index (BI) [Mahoney and Barthel, 1965] and Karnofsky Performance Scale (KPS) [Karnofsky and Burchenal, 1949] were used for the assessment of quality-of-life aspects and general performance in daily life before and after surgery as well as at every follow-up visit. The Odom score [Odom et al, 1958] and Patient Satisfaction Index (PSI) [Daltroy et al, 1996] were used to evaluate the general postoperative and follow-up outcome and subjective satisfaction.

2.2. Imaging evaluation

Evaluation of tumor location, spinal level and distribution within the spinal cord based on preoperative contrast-enhanced MR imaging. On the basis of radiographical and intraoperative observations, tumors were characterized as either dorsal or ventral of coronal spinal cord midline and as either left- or right-dominated of sagittal spinal cord midline or central; all tumors were located completely intramedullary (including both cases with the rare occurrence of completely intramedullary schwannomas). Gross-total resection was defined as complete tumor removal according to intraoperative microscopic findings and postoperative contrast-enhanced T1-weighted MR imaging. The presence and extent of edema and syringomyelia were assessed using T2-weighted and/or FLAIR MR imaging sequences.

2.3. Surgical Procedures & Neuropathological assessment

Anesthesia was performed with total intravenous anesthesia, carefully avoiding the application of muscle relaxants despite except for intubation purposes. All patients were administered steroids preoperatively (dexamethasone, intravenous single dose of 8 mg, prior to skin incision). For tumor resection, patients were placed in prone position. Via a posterior midline approach, the lamina and spinous processes overlying the tumor were exposed and either laminotomy, hemilaminectomy, laminoplasty or interlaminar fenestration was performed to provide exposure of the tumor margins. In all cases intraoperative ultrasonography was used before dural opening to assure a precise exposure of the tumor.

The midline myelotomy was performed by sharp dissection after visual identification and marking of the anatomical midline by the surgeon and confirmatory recording of both spinal SSEPs to follow tibial and/or median stimulation with an 8-channel dorsal column mapping (DCM) −electrode (AdTech Co., USA) as well as spinal cord stimulation by bipolar concentric probe (Inomed Co., Germany) with recording of cortical SSEP phase reversal at C3/C4. Resection was performed under microscope- and ultrasound-guidance according to the state-of the-art microsurgical techniques as well as with continuous multimodal IONM as described below. After termination of resection, the dura was closed

in a watertight manner and a subdural hematoma was excluded by a subsequent intraoperative ultrasonographic control before tissue and wound closure.

2.4. Intraoperative neurophysiological monitoring (IONM)

In all cases, microsurgical tumor resection was performed under continuous IONM of both SSEPs and mTcMEPs as well as D wave and free-running electromyography (frEMG). For stimulating and recording, an integrated IONM system was used (ISIS, Inomed Co., Germany). SSEPs (individual pulse width 200–500 msec, 2.7–4.7 Hz repetition rate, maximum 40 mA, at least 200 averages) were performed in median and posterior tibial nerve. For recording mTcMEPs and frEMG, subdermal pairs of electrodes were placed bilaterally and in first dorsal interosseous, abductor pollicis brevis, abductor digiti minimi, brachioradialis, biceps, triceps, deltoid as well as tibialis anterior and abductor hallucis muscles. For TES, which was applied in a medial or lateral interhemispheric fashion, stimulating electrodes were placed at C1, C3, C2, C4 (acc. to the international 10–20-EEG-system) utilizing a constant current stimulator (250 mA at 400 V maximum). mTcMEP were elicited with a monophasic anodal train-of five pulse (250 – 500 Hz, 0.5 msec individual pulse width) at a 0.5 – 1 Hz repetition rate, and D wave was elicited with single pulse (other parameters as for mTCMEP). It was assumed that monophasic anodal stimulation activates predominantly, but not exclusively, the right and left CST. For D wave, a single recording electrode (FSR03, Inomed Co., Germany) was placed epidurally and caudally to the surgical level (i.e. caudal edges of the laminotomy/-plasty/hemilaminectomy/fenestration) as well as strictly in the midline.

After patient positioning, utmost care was taken to optimize and adjust stimulation and recording parameters to obtain SSEPs, mTcMEPs and D wave responses. Baseline parameters (incl. stimulation intensity, amplitude and latency, etc.) of SSEPs, mTcMEPs and D wave were documented and were then continuously recorded in an alternating fashion throughout surgery. If mTcMEPs-related patient movement was considered disturbing during tumor microdissection, mTcMEPs were performed frequently, but only on surgeons' request (especially after manipulation of the tumor or the spinal cord) and while pausing dissection. Electrophysiological data were continuously analyzed by a technician trained in IONM and supervised by an experienced senior neurophysiologist (AS). Any IONM changes were immediately issued to the surgeons' team and the interpretation was performed interdisciplinary between the surgical and electrophysiological team.

Significant reduction in SSEPs amplitude $\geq$ 50 % and/or an increase in SSEPs latency $\geq$ 10 % as well as loss or significant decrement in mTcMEPs amplitude $\geq$ 80 % or in D Wave amplitude $\geq$ 50 % as well as significant spontaneous EMG activity (e.g. neurotonic discharges) especially during or immediately after surgical manipulation were defined as 'warning criteria of IONM' and - if technical reasons (e.g. dislocation of electrodes), anesthesiological reasons (e.g. lowering of blood pressure or body temperature, change of intravenous anesthesia management or addition of volatile anesthetics) and temporary surgical reasons (e.g. irrigation with cold saline solution) are excluded - classified as 'critical IONM changes'.

In circumstances of critical IONM changes, first technical problems were ruled out and then the most recent anesthesiological and surgical steps were reconsidered, and immediate corrective actions were initiated, e.g. cessation of additional volatile anesthetics, correction of blood pressure or modification of the surgical technique (e.g. temporary haltering of resection, reduction of traction on the tumor or surrounding tissue, irrigation with warm saline solution and/or continuation of resection at distant sites). In case of repetitive (or persistent) critical IONM changes during the resumption of tumor resection/dissection in the very same area where prior manipulation had been halted for corrective actions due to critical IONM changes, further attempts for additional tumor resection/dissection were abandoned.

For statistical analysis, critical IONM changes in SSEPs, mTcMEPs, D wave and/or frEMG monitoring were classified as either 'transient pathological' (complete resolution within surgery till dura closure) or 'permanent pathological' (persistence after dura closure) for the respective IONM modality, while no critical IONM changes were classified as 'non-pathological IONM'.

2.5. Statistical analysis

Statistical analysis was performed using Sigma Plot for Windows v.11 (Systat Software Inc., USA). Differences are defined to be statistically significant if the p value is < 0.05. For comparison of groups for differences the Student's *t*-test was used for numeric values, the Mann-Whitney Rank Sum test for ordinal variables and the χ2-test resp. Fisher's exact test (in case of 2x2-contingency tables) for nominal variables. To investigate the predictive potential of D wave, mTcMEPS, frEMG and SSEPs, intraoperative findings of the afore mentioned IONM modalities (and any combination of them) were correlated with the upper and lower extremities' motor/neurological outcome measurements as well as outcome compound scores at the above mentioned postoperative timepoints and compared; sensitivity, specifity and positive/negative predictive values (PPV/NPV) were calculated afterwards. To investigate risk factors (including patient sex/age/BMI, kind/duration of clinical symptoms and tumor location related to the myelon, etc.) associated with 1) successful obtaining of IONM baseline signals and 2) occurrence of transient/permanent critical IONM changes during tumor resection and 3) unfavourable outcome, logistic regression analyses (polytomous variables) and χ2-test resp. Fisher's exact tests (dichotomous variables) were performed.

3. Results

3.1. Patients' & tumor and operative Characteristics

Altogether 20 patients with IMSCTs above the C4/5-level were operated in our center during the 6-years observational period. Mean age was 44 years and there was a predominance of the male gender (male/female: 2.3:2). Detailed baseline patients' and tumor characteristics are displayed in Table 1.

Gross-total resection was accomplished in 90 % of the cases according to intraoperative findings and postoperative contrast-enhanced MRI. Mean operative time was 234 $\pm$ 66 min. and mean blood loss 310 $\pm$ 205 ml. Mean in-patient stay was 7 $\pm$ 3 days.

3.2. Detailed Neurological, functional and quality-of-life outcome

Detailed neurological status including fine-motor and complex functional performance of distal and proximal upper and lower extremities' function at the preoperative timepoint as well as at discharge and during long-term follow-up (mean 29.5 $\pm$ 18.8) are shown in Table 2.

Postoperatively new or worsened motor deficits occurred most often in the proximal upper extremities (23 %) reflecting the segments of the lesion/surgery in the high-cervical spinal cord, but were transient in the vast majority (78 %). Postoperatively new or worsened motor deficits occurred in the distal upper extremities in 20 % and in the lower extremities in 13 % and were of transient nature in 63 % and 60 %. Except for one postoperatively severely worsened permanent left proximal upper extremity paresis (deterioration in deltoid muscle motor function of MRC grade 3), all permanent postoperatively new or worsened motor deficits were only mild (deterioration in motor function of MRC grade 1 or 2) and there was no case with a postoperative new plegia.

Sensory changes were the most frequent permanent postoperatively new neurological deficits both in the upper and lower extremities (25 % and 28 %) and mainly comprised of hypoesthesia and impairment of epicritical sensibility.

Distal upper extremities fine-functional status was assessed by

TABLE 1
Baseline characteristics at admission for surgery.*.

Characteristics	Patients (n = 20)
gender, male/female	14 / 6
mean age, yrs	44 ± 18
comorbidities**, no. (%)	
cardiovascular diseases	2 (10.0)
peripheral neuropathy	2 (10.0) [carpal tunnel syndrome]
nicotine dependence	3 (16.7)
obesity	5 (25.0)
BMI, kg/m^2	26.1 ± 4.2
preoperative symptoms, no. (%)	
motor deficit	8 (40.0)
spasticity	4 (20.0)
sensory deficit	14 (70.0)
gait ataxia	7 (35.0)
vegetative symptoms	3 (15.0)
pain	7 (35.0)
mean duration of symptoms, mos	20.3 ± 36.1
tumor entity***, no. (%)	
ependymoma (WHO °II)	6 (30.0)
pilocytic astrocytoma, WHO °I	1 (5.0)
glioblastoma, WHO °IV	1 (5.0)
diffuse midline glioma, WHO °IV	2 (10.0)
schwannoma, WHO °I	2 (10.0)
hemangioblastoma, WHO °I	6 (30.0)
cavernoma	1 (5.0)
other	1 (5.0) [dual lesion: capillary hemangioma and neuroma]
location of tumor, no. (%)	
C1/2 level	4 (20.0)
C2/3 level	3 (15.0)
C3/4 level	7 (35.0)
C4/5 level	6 (30.0)
extent of tumor, no. (%)	
singel-level	17 (85.0)
two-level	3 (15.0)

* Mean values are presented ± standard deviation.
** None of the patients suffered from diabetes mellitus, polyneuropathy or alcohol abuse.
*** based on the 2016 WHO classification of CNS tumors or head/neck tumors or respective classification systems.[Louis et al., 2016], [El-Naggar, 2017].

NHPT, which reflects the complex interaction of motor and sensory function for the usability of the hand, and remained stable or improved (compared to the preoperative status) in 45 % of the monitored limbs after surgery and during long-term follow-up. In up to 40 % of the monitored limbs, there was a transient significant clinical deterioration in NHPT assessment after surgery which improved afterwards to attain the preoperative status (or better) during long-term follow-up. However, in 15 % of the monitored limbs, there was a significant clinical deterioration in NHPT assessment after surgery which did not resolve (n = 3 limbs) or even further worsened (n = 3 limbs, due to progression of the underlying spinal cord tumor disease) during long-term follow-up.

Distal lower extremities functional status was respectively assessed by gait disturbances/ataxia and was stable or improved in 60 %, transiently affected in up to 30 % and permanently affected in 10 % of the cases after surgery compared to the preoperative status.

Gross-functional status and quality-of-life data preoperatively as well as at discharge, 3- and 6-month follow-up as well as last follow-up are displayed in Table 3. In general, there was a significant decrease in the functional status as well as physical component of quality-of-life perception directly after surgery which disappeared completely until the 3-month follow-up point and stayed stable on the level of the preoperative status/perception during the further follow-up period. Only the mental component of quality-of-life perception was slightly improved directly after surgery and stayed stable on the level of the preoperative perception for the further follow-up observations.

3.3. *Predictive value of IONM modalities and IONM performance*

Intraoperative findings of the distinct IONM modalities with the corresponding detailed neurological outcome for each monitored limb can be found in **Supplementary Table 1** for the upper extremities and in **Supplementary Table 2** for the lower extremities.

D wave monitoring was feasible in all cases and included monitoring of the distinct spinal MEPs predominantly reflecting the left and right CST individually. D wave monitoring was stable without any intraoperative critical changes (amplitude loss > 50 % from baseline) in 16/20 patients (80 %), while transient changes (with transient amplitude loss > 50 % from baseline) occurred in one patient for the left CST and two patients for the right CST and one patient for both CST; there was no patient with a permanent critical deterioration (amplitude loss > 50 % from baseline) of D wave. Detailed D wave status at the end of surgery was as follows: one patient had a D wave amplitude decrement of 20 %–49 % from baseline for the left CST and two patients for the right CST and one patient for both CST, while one patient had a D wave amplitude decrement of 1 %–19 % from baseline for the left CST and two patients for the right CST and five patients for both CST; in the other patients D wave amplitude was stable or improved in comparison to the baseline values. In summary, neither D wave for both, nor left or / and right CST showed a combined alteration > 50 %, meaning that no permanent critical D-wave change occurred.

One of the patients had a postoperatively severely worsened permanent left deltoid muscle paresis and corresponding severe persistent/pathological spontaneous activity (PSA) with neurotonic discharges in deltoid-muscle-EMG during tumor resection suggesting a direct lesion of

TABLE 2
Detailed neurological and fine-motor/functional status with postoperative outcome*.

Characteristics	preoperative deficit (baseline)	postoperatively unchanged or improved status	transient new postoperative deficit	permanent new postoperative deficit
motor function (n = 40 limbs)				
hand (intrinsic + distal forearm), no. (%)	12 (30.0)	32 (80.0)	5 (12.5)	3 (7.5)
proximal upper extremity, no. (%)	8 (20.0)	31 (77.5)	7 (17.5)	2 (5.0)
lower extremity, no. (%)	3 (7.5)	35 (87.5)	3 (7.5)	2 (5.0)
sensory function (n = 40 limbs)				
upper extremity, no. (%)	18 (45.0)	28 (70.0)	2 (5.0)	10 (25.0)
lower extremity, no. (%)	9 (22.5)	27 (67.5)	2 (5.0)	11 (27.5)
complex distal upper extremities‘ function (n = 40 limbs)				
nine-hole peg test, no. (%)	29 (72.5)	24 (60.0)	10 (25.0)	6 (15.0)
manometrical hand-force, no. (%)	12 (30.0)	28 (70.0)	7 (17.5)	5 (12.5)
complex central and lower extremities‘ function (n = 20)				
gait disturbance/ataxia, no. (%)	7 (35.0)	12 (60.0)	6 (30.0)	2 (10.0)
vegetative function, no. (%)	3 (15.0)	19 (95.0)	1 (5.0)	0 (0.0)

TABLE 3
Gross-functional status and quality-of-life with postoperative outcome.*.

Characteristics	Patients (n = 20)	p-value vs. preoperative
McCormick score, median (range)		
preoperative	1 (1 – 4)	/
at discharge after operation	2 (1 – 4)	0.021
at 3-month follow-up	1 (1 – 4)	0.586
at 6-month follow-up	1 (1 – 4)	0.586
at last follow-up	1 (1 – 4)	0.718
mJOA, median (range)		
preoperative	16 (8 – 18)	/
at discharge after operation	13 (7 – 18)	0.011
at 3-month follow-up	15 (9 – 18)	0.784
at 6-month follow-up	14 (6 – 18)	0.229
at last follow-up	15 (7 – 18)	0.503
Barthel Index, median (range)		
preoperative	100 (40 – 100)	/
at discharge after operation	100 (25 – 100)	0.003
at 3-month follow-up	100 (50 – 100)	0.474
at 6-month follow-up	100 (40 – 100)	0.672
at last follow-up	100 (40 – 100)	0.524
Karnofsky Performance Index, median (range)		
preoperative	90 (40 – 100)	/
at discharge after operation	70 (40 – 90)	0.010
at 3-month follow-up	80 (50 – 100)	0.603
at 6-month follow-up	90 (50 – 100)	0.994
at last follow-up	80 (60 – 100)	0.684
Short Form −36 Health Survey – Physical Compound Score, mean		
preoperative	45.8 ± 11.5	/
at discharge after operation	35.8 ± 10.0	0.006
at 3-month follow-up	44.6 ± 11.5	0.744
at 6-month follow-up	46.0 ± 12.0	0.958
at last follow-up	46.4 ± 10.8	0.858
Short Form −36 Health Survey – Mental Compound Score, mean		
preoperative	43.4 ± 11.6	/
at discharge after operation	47.6 ± 13.0	0.282
at 3-month follow-up	44.8 ± 12.0	0.716
at 6-month follow-up	44.7 ± 11.3	0.727
at last follow-up	44.6 ± 11.5	0.738
Odom score, median (range)		
at discharge after operation	4 (1 – 4)	/
at 3-month follow-up	3 (1 – 4)	/
at 6-month follow-up	3 (1 – 4)	/
at last follow-up	3 (1 – 4)	/
Patient Satisfaction Index, median (range)		
at discharge after operation	2 (1 – 4)	/
at 3-month follow-up	1 (1 – 4)	/
at 6-month follow-up	1 (1 – 4)	/
at last follow-up	1 (1 – 4)	/
mean duration of last follow-up, months	29.5 ± 18.8	/

* Mean values are presented ± standard deviation.

the anterior horn or the C5 spinal root (which was not covered by the modality of D Wave monitoring). More important, none of the patients had any severe permanent postoperative motor deficits for the distal upper as well as lower extremities and every patient was ambulatory at last follow-up which proves that D wave can safely monitor and predict long-term gross-motor function for all covered spinal cord segments.

However, even for the spinal cord segments anatomically covered for monitoring, D wave was not able to predict any immediate post-operative new or worsened motor deficits of transient nature (hand: 13 %; lower extremities: 8 %) and also not any new or worsened mild motor deficit of permanent nature (hand: 8 %; lower extremities: 5 %). This was true for the cut-off of > 50 % amplitude decrement (as employed intraoperatively) as threshold for dichotomization in critical and non-critical permanent D wave changes, but also when statistically analyzing the data post hoc with the cut-off of > 20 % amplitude decrement as threshold for dichotomization in critical and non-critical permanent critical permanent D wave changes.

However, performance of mTcMEPs for prediction of postoperative detailed motor function was also poor with a high rate of false-positive and a low rate of true-positive findings. Sensitivity, specificity, PPV and NPV of mTcMEPs for motor outcome of the hand (intrinsic + distal forearm), proximal upper extremity as well as lower extremity with regard to the occurrence of immediate postoperative new motor deficits as well as persisting motor deficits during long-term follow-up are

TABLE 4
mTcMEPs, EMG and SSEPs performance for prediction of immediate post-operative and long-term detailed neurological and fine-motor/functional outcome.

Characteristics	Sensitivity	Specificity	FP	FN	PPV	NPV
mTcMEPs for immediate postop. motor deterioration						
hand (intrinsic + distal forearm)	0.0	84.4	100.0	22.9	0.0	77.1
proximal upper extremity	11.1	87.1	80.0	22.9	20.0	77.1
lower extremity	0.0	91.4	100.0	13.5	0.0	86.5
mTcMEPs for long-term postop. motor deterioration						
hand (intrinsic + distal forearm)	0.0	86.5	100.0	8.6	0.0	91.4
proximal upper extremity	50.0	92.1	75.0	2.8	25.0	97.2
lower extremity	0.0	92.1	100.0	5.4	0.0	94.6
EMG for immediate postop. motor deterioration						
proximal upper extremity	33.3	83.9	62.5	18.7	37.5	81.3
EMG for long-term motor deterioration						
proximal upper extremity	100.0	84.2	75.0	0.0	25.0	100.0
SSEPs for immediate postop. sensory deterioration						
median nerve −> upper extremity	33.3	92.9	60.0	43.3	66.7	76.5
tibial nerve −> lower extremity	0.0	84.6	100.0	38.9	0.0	61.1
SSEPs for long-term sensory deterioration						
median nerve −> upper extremity	40.0	93.3	33.3	17.6	66.7	82.4
tibial nerve −> lower extremity	0.0	86.2	100.0	30.6	0.0	69.4
multimodal IONM for immediate postop. complex fine- functional deterioration						
hand (NHPT)	23.5	73.9	60.0	43.3	40.0	56.7
gait disturbance / ataxia	42.9	69.2	57.1	30.8	42.9	69.2
multimodal IONM for long-term complex fine-functional deterioration						
hand (NHPT)	42.9	78.8	70.0	13.3	30.0	86.7
gait disturbance / ataxia	50.0	66.7	85.7	7.7	14.3	92.3

displayed in Table 4. While frEMG monitoring had no impact for the prediction of motor outcome of the distal upper and the complete lower extremity due to anatomical reasons, prediction of the proximal upper extremity's motor outcome by frEMG monitoring was more accurate than with mTcMEPs monitoring, but still limited (see Table 4).

Sensory changes were the most frequent transient and permanent postoperatively new neurological deficits both in the upper and lower extremities in more then one quarter of the cases and SSEPs monitoring showed a high specificity (>85 %) for postoperative deterioration of sensory status. Overall, the predictive value of median-nerve-SSEPs changes for upper extremity's sensory outcome was better than that of tibial-nerve-SSEPs for lower extremity's sensory outcome, but still associated with a high rate of false-positive cases (up to 60 % vs. 100 %). Details are shown in Table 4.

Overall, the combination of all IONM modalities (multimodal IONM) for predicting the postoperative distal upper extremity's and lower extremity's complex fine-functional status (NHPT vs. gait disturbances/ataxia) showed a high specificity and NPV with 79 % vs. 67 % and 87 % vs. 92 %, a moderately good sensitivity of 43 % vs. 50 %, but still a high false-positive rate with 70 % vs. 86 % (see Table 4).

Table 5 combines the correlation of intraoperative changes in motor pathway monitoring (D Wave and/or mTcMEPs) with postoperative changes in detailed (fine-)motor status of the distal upper extremities in terms of a 3x3-contingency table ($p = 0.927$), while Table 6 combines the correlation of intraoperative changes in any modalities of the multimodal IONM (D Wave, mTcMEPs, frEMG and/or SSEPs) with postoperative changes in fine-functional status of the hands (NHPT; $p = 0.344$).

4. Discussion

Today, mTcMEPs and D wave are considered to be the intraoperative standard to monitor the integrity of motor function during IMSCT surgery. Since the hallmark paper of Kothbauer et al. [Kothbauer et al, 1998], a stable and unaffected intraoperative course of mTcMEPs monitoring indicates an intact motor function while intraoperative loss of mTcMEPs indicates a temporary loss of motor function in the corresponding limb as long as D wave amplitude did not decline below 50 % of the baseline value. Further decline of the D wave amplitude could indicate permanent severe motor deficit for the lower extremities. As it is well known that, although mTcMEPs loss usually indicates a postoperative deterioration of motor function, about 10 % of cases exhibit false positive mTcMEPs results (i.e., patients with intraoperative mTcMEPs loss but without any motor deficits after surgery) [Kothbauer et al, 1998; Sala et al, 2007], D wave monitoring with its unique features has to be considered as the most accurate and powerful tool for intraoperative assessing the CST integrity and therefore prediction of postoperative voluntary motor function. Since then, these principles of combined motor evoked potential data interpretation have gained broad acceptance in the community and subsequent publications have proven this interpretation to be accurate for the gross-motor outcome of the lower extremities and ability to ambulate [Deletis and Sala, 2008a; Costa et al, 2013; Sala et al, 2007; MacDonald, 2017; Sala et al, 2006; Kothbauer et al, 1997; Verla et al, 2016; Scibilia et al, 2016; Park and Hyun, 2015]. Our data also confirm this 'D wave dogma' with none of the patients showing any severe permanent postoperative motor deficits for the lower extremities and every patient being ambulatory at last follow-up despite intraoperative permanent critical lower limbs' mTcMEPs findings, but stable D wave monitoring. In combination with our high gross-total resection (90 %) and the favorable clinical outcome in compound scores like the McCormick Scale (median at last follow-up: 1), which is both in line with recent series on surgically treated IMSCTs [Salari et al, 2021; Hussain et al, 2020; Rashad et al, 2018], this underlines the high validity and reliability of our data.

However, up to today, none of the previous studies so far have addressed (and it therefore remains unknown) if the above mentioned 'D wave dogma' for the gross-motor outcome of the lower extremities also applies for the gross-motor outcome of the distal upper extremities in cases where D wave has been placed in the upper cervical spinal cord and should therefore cover the integrity of those CST fibers conveying the corresponding information for at least the forearm and hand-muscles. Moreover, as D wave alarm criteria of > 50 % amplitude reduction is proven for gait function, one might possibly expect a disproportionate loss of distal limb, pyramidal-fibre-dependent function within such non-alarm losses which might contribute to deterioration of complex hand function. Our study particularly addresses this so far unresolved question as it is the first prospectively designed study to only include those patients harbouring IMSCTs above the C4/5 level where D wave was intraoperatively placed epidurally to safely cover the segment of C5 and below. We could show that D wave monitoring was feasible and stable (without any permanent or critical changes in terms of amplitude reduction > 50 % from baseline) during surgery in all our consecutively included patients and, more important, none of the patients had any permanent deterioration in gross-motor function of the distal upper extremities during the postoperative long-term course. Moreover, also in line with the above mentioned 'D wave dogma', D wave was not able to predict any immediate postoperative new or worsened motor deficits of transient nature for the distal upper extremities (which occurred in 13 % of our patients). Altogether, we conclude that the above mentioned 'D wave dogma' seems also to be accurate for the distal upper extremities' gross-motor function and therefore to be true for all spinal cord segments anatomically covered by D wave for monitoring.

However, it is important to bear in mind that gross-motor outcome is only one aspect that affects the functional and health-related quality of life long-term outcome of patients after IMSCT resection and fine-motor as well as complex-functional status (as a complex interaction of motor/sensory function) might play an important role in this regard [Sala et al, 2022; Tufo et al, 2023]. Nevertheless, as recently outlined by the review of Liu et al. [Liu et al, 2023], there is no uniform standard for evaluation of postoperative motor outcome and virtually none of the studies, evaluating the predictive value of D Wave (or mTcMEPs) for motor outcome so far, have decidedly assessed or addressed the detailed fine-motor neurological and complex-functional outcome exceeding the graduation into coarse compound scores (e.g. McCormick scale) or the mere dichotomization in ambulatory or not. This is true for both the lower extremities as well as particularly for the distal upper extremities including the indispensable hand function. Both, the lack of a uniform standard (and timepoint) for postoperative motor outcome assessment

TABLE 5
IONM and postoperative fine-motor outcome for the distal upper extremities (n = 40 limbs).

Characteristics		intraoperative D Wave / TcMEPs changes		
		no	transient	permanent
postoperative fine-motor deficits, no.	no	22	6	5
	transient	3	1	0
	permanent	2	1	0

TABLE 6
IONM and postoperative fine-functional (NHPT) outcome for the distal upper extremities (n = 40 limbs).

Characteristics		intraoperative multimodal IONM changes (D Wave / TcMEPs / frEMG / SSEPs)		
		no	transient	permanent
postoperative fine-functional (NHPT) deficits, no.	no	21	2	1
	transient	10	0	0
	permanent	4	2	0

and, for mTcMEPs, the still controversial debated alarm threshold (ranging from > 50 % amplitude reduction to all-or-nothing principle) might contribute to the enormous range of reported sensitivity, specifity and FP and FN rates for intraoperative motor evoked potential monitoring (ranging between as low as nearly 0 % to as high as 100 % between previous publications) and therefore limits the predictive significance of intraoperative motor evoked potential monitoring for clinical implications [Liu et al, 2023].

More important, the up-to-date lack of studies assessing the detailed fine-motor neurological and complex-functional outcome renders the predictive value of D Wave and mTcMEPs monitoring in this regard to be wildly unknown so far. We believe this to be essential as we have seen in our series, which prospectively assesses both compound scores (e.g. McCormick scale as in the vast majority of previous studies) as well as detailed fine-motor neurological outcome (e.g. MRC grade 1 paresis) and complex-functional status (e.g. NHPT), that in up to 18 % resp. 30 % of the patients there are significant deteriorations in fine-motor resp. complex-functional status for the distal upper extremities without reaching a level to qualify for change in McCormick Score. We could show that surgery-related deterioration of detailed fine-motor function at last-follow-up was still present in 8 % for the distal upper extremities (and also in 5 % for the lower extremities), while D wave did not show any critical changes in the intraoperative course. This was true for both the 'traditional' cut-off of > 50 % amplitude decrement as threshold for critical permanent D wave changes, but also for a more narrow cut-off of > 20 % amplitude decrement (in a post-hoc analysis) addressing the idea of a disproportional loss of distal limb, pyramidal-fiber-dependent function within 'non-alarm losses' of < 50 % amplitude reduction for the 'traditional' cut-off (for gait function). This suggests that D wave is not able to sufficiently predict the precise fine-motor outcome of the segments anatomically covered. mTcMEPs might help in this situation: with a high specificity of up to 92 % and a high NPV of up to 97 %, we could prove in our study the assumption of Kothbauer et al. [Kothbauer et al, 1998], that unaffected intraoperative course of mTcMEPs monitoring indicates an intact motor function, to be also true for the fine-motor outcome of the hands and distal forearm. However, mTcMEPs' sensitivity was very low and the rate of false-positives findings very high for both transient and permanent nature suggesting that fine-motor function of the hands might still be a challenge to monitor. This might partly be anatomically explained as the completion of voluntary fine movements requires the simultaneous balance of both sensory and motor functions and it not only involves the CST, but might also need the co-participation of the tectospinal, rubrospinal, reticulospinal, and vestibulospinal tracts [Malhotra, 2010]. However, MEPs only monitor the function of the corticospinal tract, which might be one of the reasons for the high rate of false-positives [Liu et al, 2023]. This seems specifically apply for the detailed fine-motor function of the filigree hand movements – and even more for complex hand functions as measured in complex-functional hand tests like the NHPT, which assesses the complex interaction of motor and sensory function for the hands' usability. There are also no reliable and easy-to-use methods to estimate the amount of conductive fibers and their synchronicity preoperatively. This, and the difficulty in distinguishing between transient and permanent signal changes, emphasizes that D wave and mTcMEPs are semi-quantitative methods. From the perspective of IONM this explains the variability of signal alteration and postoperative motor function. Nevertheless, we are convinced that multimodal IONM is of particular necessity for monitoring such complex hand functions and we could detect a high specificity and NPV of 79 % and 87 % as well as a good sensitivity of 43 % in our study when all IONM modalities were taken into account in terms of a multimodal IONM approach. For complex hand function not only proprioceptive, but also epicritic sensibility is necessary, which is not fully assessed by SEP. This also explains the low sensitivity for the prediction of all sensory deficits. To make it even more complex: while we did not see any secondary deterioration between the postoperative and last follow status with regard to MRC motor strength or surface sensibility in any of our patients, there were two patients with a secondary deterioration in the postoperative and last follow NHPT status (in only one hand each). This prompts the conclusion that the complex interaction of motor and sensory function for the hands' usability might involve additional factors not yet readily determined and therefore makes the intraoperative monitorability even more challenging.

In analogy to the complex-functional outcome of the hand usability, monitoring of the complex-functional outcome of the lower extremities (assessed by detailed assessment of gait disturbances) with multimodal IONM is also similarly viable with a high specificity and NPV of 67 % and 92 % as well as a good sensitivity of 50 %. We therefore strongly agree with recent reviews determining multimodal IONM with D wave, TcMEPs, SSEPs and frEMG monitoring as the today's best available option to monitor the holistic functional integrity of the spinal cord during IMSCT surgery [Liu et al, 2023; Sala et al, 2022] and are the first to underline this with prospectively assessed detailed data (with focus on the distal upper extremities) collected in a large homogeneous series of patients undergoing high-cervical IMSCTs resection with multimodal IONM.

Limitations of our study are manly owed to the overall small sample size given the overall very low incidence of high-cervical intramedullary spinal cord tumors. Moreover, there was no case of intraoperatively complete loss of D wave signals in our series restricting the power of statistical D wave performance assessment. Furthermore, because we prospectively deployed full multimodal IONM in every patient, it is not possible to completely eliminate the interaction of these modalities during the course of intraoperative decisions; for example, one may see an EMG discharge or SSEPs decrease, following which a request is made for immediate mTcMEPs. Therefore, to stipulate that D wave monitoring predicts one thing and SSEPs or EMG predicts another thing independently requires a major assumption of no or very limited interaction among tests which is not entirely given in case of state-of-the-art multimodal IONM.

5. Conclusions

Our prospective study on high-cervical IMSCT surgery is the first to indicate that D wave can safely monitor the functional integrity of the CST and can reliably predict the gross-motor outcome of all spinal segments anatomically covered including the hands and forearms. However, D wave fails to sufficiently cover distal upper extremities' detailed fine-motor outcome in the short- and long-term follow-up. mTcMEPs might help in this situation since the unaffected intraoperative course of mTcMEPs monitoring indicates an intact fine-motor status for the hands and distal forearms, but have the drawback of a very low sensitivity and high false-positive rate which might be a correlate that voluntary fine movements of the hand requires the simultaneous balance of both sensory and motor functions and not only involves the CST. Therefore, particularly the intraoperative monitoring of the complex-functional status of the hands and distal forearms (which reflects the complex interaction of motor/sensory function for the hand usability) is only viably possible with multimodal IONM which may provide a high specificity and NPV as well as a good sensitivity, but still remains a challenge even with todays' various monitoring modalities.

Presentation at a conference.

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Data statement

The data that support the findings of this study are not openly available request. The data that support the findings of this study are not openly available due to restrictions because of legal and ethical reasons and are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.10.007.

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