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Postoperative navigated transcranial magnetic stimulation to predict motor recovery after surgery of tumors in motor eloquent areas

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HIGHLIGHTS

- We discuss the predictability of reversibility of motor deficits after supratentorial tumor surgery.
- We describe early postoperative MRI navigated TMS as reliable tool to predict motor recovery.
- Postoperative nTMS may clarify the potential for recovery in case of intraoperative MEP alterations.

ABSTRACT

Objective: To know whether motor deficits after tumor surgery are transient is reassuring for the patient and crucial for planning rehabilitation and adjuvant treatment. We analyze the value of postoperative MRI navigated transcranial magnetic stimulation (nTMS) compared to intraoperative MEP monitoring in predicting recovery of motor function.
Methods: Retrospective series of nTMS mappings within 14 days after surgery for supratentorial tumors (09/2014–05/2018). All patients with motor deficits of Medical-Research-Council-Grade (MRCS) 0–4- were included.
Results: We performed nTMS mapping on average 3.8 days after surgery and recorded nTMS MEP in 11 of 13 patients. Motor strength recovered to at least MRCS 4 within one month if postoperative nTMS elicited MEPs (positive predictive value 90.9%). If nTMS did not elicit MEPs, the patient did not recover (negative predictive value 100%). Intraoperative MEP and postoperative nTMS were equally predictive for long-term motor recovery. In cases of intraoperative MEP alteration/signal loss, but a positive postoperative nTMS mapping, 2/3 patients demonstrated a good motor recovery.
Conclusion: nTMS may predict long-term motor recovery of patients suffering from severe motor deficits directly after resection of tumors located in motor eloquent areas.
Significance: In cases of intraoperative MEP alterations, postoperative nTMS may clarify the potential for motor recovery.

1. Introduction

Removing the last and deepest part of a tumor near an eloquent area potentially puts neurological functions at risk. The oncological advantage of a more radical resection (Lacroix et al., 2001, Stummer et al., 2006, McGirt et al., 2009, Sanai et al., 2011, Jakola et al., 2012, Salvati et al., 2012) may be counterbalanced by increasing risks of neurological deficits (Schucht et al., 2014).

Tumor resection might be guided by intraoperative electrical stimulation (De Witt Hamer et al., 2012). Intraoperative cortical mapping is considered the gold standard to localize motor function and might help to preserve the primary motor cortex (M1)

Abbreviations: CST, corticospinal tract; Cing, Cingulum; CUSA, Cavitron Ultrasonic Surgical Aspirator; DCS MEP, direct cortical stimulation elicited MEP; DPM, dorsal premotor area; IOM, intraoperative neurophysiological monitoring; M1, primary motor area; MRCS, Medical Research Council Scale; MEP, motor evoked potential; MT, motor threshold; nTMS, navigated transcranial magnetic stimulation; RMT, resting motor threshold; SMA, supplementary motor area; TES MEP, transcranial electrical stimulation elicited MEP; VPM, ventral premotor area.

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(Penfield et al., 1937, Merton et al., 1980, Berger et al., 1989, Ebeling et al., 1992, Duffau, 2005, Seidel et al., 2012). Intermittent subcortical mapping of the corticospinal tract (CST) with a hand-held probe is used to localize motor tracts in deep white matter structures at different stages of tumor resection (Berger et al., 1989, Duffau, 2005, Bello et al., 2008). Continuous dynamic subcortical stimulation via a surgical instrument like the suction probe or Cavitron Ultrasonic Surgical Aspirator (CUSA) may further improve the surgical workflow (Raabe et al., 2014, Shiban et al., 2015, Roth et al., 2017). Continuous monitoring of motor evoked potentials (MEPs) enables real-time assessment of the functional integrity of the CST (Deletis et al., 2001a, Sala et al., 2003, Neuloh et al., 2007).

However, neurological deficits may still occur despite the advances in mapping techniques (Seidel et al., 2013) and postoperative deficits have detrimental effects on patients' quality of life and survival (McGirt et al., 2009). Knowing whether a postoperative deficit is transient or permanent is essential not only for the patient but also for the neurosurgeon, physiotherapist and oncologist. Signal alterations during intraoperative MEP monitoring may predict permanent motor deficits (Deletis et al., 2001a; Neuloh et al., 2007; Kombos et al., 2009; Krammer et al., 2009; Szelényi et al., 2010; Krieg et al., 2012; Seidel et al., 2013). However, in 25% of patients with intraoperative MEP loss, motor function still recovers (Seidel et al., 2013). Navigated transcranial magnetic stimulation (nTMS) is a validated non-invasive method to assess motor function (Rossini et al., 2015, Tarapore et al., 2016, Krieg et al., 2017, Takakura et al., 2017).

The objective of the present study was to analyze the value of postoperative nTMS in predicting the recovery of motor function. Furthermore, the benefit of postoperative nTMS as a supplement to intraoperative neurophysiological MEP monitoring was assessed.

2. Methods

2.1. Study design

This retrospective study was conducted with the approval of the local ethics committee (Project-ID 2017-02126) and the Declaration of Helsinki.

We retrospectively identified patients who underwent postoperative nTMS mapping within 14 days after surgery for a supratentorial tumor between September 2014 and May 2018. Patients were included in this study if they had a postoperative motor deficit of Medical Research Council Scale (MRCS) grade 0 to 4-, regardless of presurgical motor function. In case a patient demonstrated a paresis in more than one extremity, the more severely affected extremity was chosen for further analysis. If upper and lower extremity were equally affected, the upper extremity was chosen. Patients without reliable intraoperative MEP responses available were excluded from analysis.

The primary endpoint of our study was good motor recovery 1 month after surgery. Good motor recovery was defined as muscle strength of MRCS grade 4–5 by manual assessment. We hypothesized that a positive MEP response in a paretic limb elicited by nTMS mapping within 14 days after surgery would predict attainment of the primary endpoint.

2.2. Clinical evaluation

Motor function was evaluated before surgery, as well as one day, one week, and one month after surgery by a board-certified physician. The motor function was assessed with manual muscle testing using the MRCS grading for each limb individually. Grade 0 indicated no movement at all, while grade 5 denoted normal contraction against full resistance. Grades 0 to 4- were considered a poor outcome, while grades 4–5 were considered good recovery. All patients underwent intensive physiotherapy and neurorehabilitation after surgery.

2.3. Surgical procedure and intraoperative neurophysiological monitoring

For all procedures, total intravenous anesthesia was maintained with propofol and remifentanyl. A short-acting muscle relaxant (Esmeron) was administered for induction only. The "train-of-four" technique was used to test recovery from muscle relaxation. For intraoperative neurophysiological monitoring and mapping, we used the ISIS system (Inomed Co.) equipped with a constant-current stimulator (OSIRIS). For MEP monitoring, whenever possible, stimulation was performed over a strip electrode placed on the precentral gyrus, or this electrode was slid under the craniotomy with the help of neuronavigation (direct cortical stimulation [DCS] MEP). For continuous subcortical mapping, monopolar cathodal short-train stimulation (5 stimuli, 0.5 msec pulse duration, interstimulus interval 4.0 msec) over our recently introduced electrified suction device was applied (so called continuous dynamic mapping technique) (Raabe et al., 2014). Subdermal needle electrodes were placed at least in the following contralateral muscles for MEP recording: M. biceps brachii (BIC), M. extensor carpi radialis (EXT), M. abductor pollicis brevis (APB), M. tibialis anterior (TA) and M. abductor halluces (AH) and an ipsilateral control (ipsilateral APB). The motor threshold (MT) was defined as the stimulation intensity that elicited MEPs from the target muscle at a minimum amplitude of 50 μV within four consecutive trains at a 0.5 Hz repetition rate. Our intraoperative neurophysiologic monitoring and mapping techniques have previously been described in detail (Seidel et al., 2012, Schucht et al., 2013, Seidel et al., 2013, Raabe et al., 2016). During intraoperative MEP monitoring all muscles of interest (according to the tumor location) were observed and a warning was given as soon as the recording of already one muscle showed significant alterations.

Patients received 5-aminolevulinic acid (5-ALA) if a malignant glioma was suspected. Glioma resection was continued until proximity to motor eloquent areas was indicated by the neurophysiological mapping or until all 5-ALA fluorescent tissue was removed (Schucht et al., 2013, Seidel et al., 2013, Raabe et al., 2014, Schucht et al., 2014).

2.4. Postoperative nTMS motor mapping

3D T1-weighted gradient-echo sequence magnetized prepared rapid gradient echo (MP-RAGE) images performed with a 1.5- or 3-Tesla MRI System (Siemens) were acquired within 48 hours postoperatively and used for the postoperative nTMS neuronavigation.

All postoperative nTMS examinations were done within 14 days after surgery. The nTMS system used in this study included a magnetic stimulator with a figure-of-eight TMS coil (Nexstim 4.3). The navigation device oriented individual 3D-MRI data to the patient's head through infrared tracking (Polaris Spectra) using spheres coated with a reflective surface. While applying nTMS, muscle activity was continuously monitored using electromyography (EMG) with surface electrodes (Ambu Neuroline) over the muscle bellies and the tendons of the contralateral M. extensor carpi radialis (EXT), M. abductor pollicis brevis (APB), M. tibialis anterior (TA) and M. abductor halluces (AH). A ground electrode was placed on the ipsilateral elbow over the olecranon. The nTMS device triggered the EMG recording system. The presumed hot spot of arm and leg muscles was determined accordingly to anatomical landmarks (omega sign of precentral gyrus for the hand muscles;

interhemispheric fissure of the precentral gyrus for leg muscles) guided by early postoperative MRI which could identify displaced motor cortex by tumor growth or brain shift into the resection cavity. A rough mapping was performed and extended along the central sulcus medially and laterally using the same intensity until MEPs disappeared while the coil orientation was kept perpendicular to the central sulcus. The site eliciting maximum MEP defined the hot spot and then used for defining the resting motor threshold (RMT) (Krieg et al., 2017). A muscle response with a peak-to-peak amplitude above 50 μV was considered positive. RMT was defined as the lowest intensity eliciting 5 positive responses out of 10 stimulations (Rossini et al., 2015, Krieg et al., 2017). RMT was measured for each limb individually. Stimulator output was increased stepwise until MEP could be elicited (Tarapore et al., 2016). We classified the result as "MEP loss" if not five MEP out of 10 stimulations (RMT) could be elicited with 70–100% of stimulator output. For further analysis in predicting motor recovery of the patient, the clinical more severely affected extremity was chosen and compared to the ability to obtain a MEP at RMT of this extremity.

2.5. Statistical analysis

The primary outcome was assessed as a binary variable. Sensitivity and specificity as well as positive and negative predictive value of a positive nTMS MEP response were calculated. Distance of the tumor boundary to the corticospinal tract and to M1 was measured using the Brainlab software and diffusion tensor imaging fiber tracking.

3. Results

3.1. Subjects

Between September 2014 and May 2018, 140 nTMS examinations for motor function were performed in our department. Of those, 30 examinations were done after surgery. Inclusion criteria (nTMS within 14 days after surgery, postoperative motor impairment score below MRCS 4, reliable intraoperative MEP responses available) were met by 13 patients: all patients presented with hemiparesis and none with monoparesis. In four of these 13 patients, the leg was more severely affected and chosen for analysis; whereas in five the arm was more affected. In the remaining four patients, the upper and lower extremity were equally affected and the upper extremity was chosen for analysis in these cases. Five of the 13 patients already suffered from a preoperative motor deficit (see below).

The mean age of patients was 51.4 years. Five patients were female and eight were male. Histopathology revealed high-grade glioma in nine and low-grade glioma in three patients, as well as one metastasis. Tumor location with respect to motor eloquence is displayed in the Table 1.

Intraoperatively, a complete loss of DCS MEP occurred in three patients, while two patients showed a significant motor threshold increment or amplitude reduction of over 50%, which was not reversible with any maneuver (see below). DCS MEP remained without any significant changes in eight patients. Early postoperative MRI showed no major ischemic injury in any of the patients.

3.2. Postoperative clinical findings

Of the 13 patients analyzed, two presented with grade 3, three with grade 2, one with grade 1–2, one with grad 1 and six with grade 0 paresis on the first day after surgery (see Table 1). In all patients, motor function was worse postoperatively than preoperatively. One month postoperatively, ten patients (76.9%) had recovered to muscle strength of MRCS 4 or 5, while three patients continued to show significant paresis scoring MRCS 4- or worse. Details of the muscle strength of each patient are given in the Table 1. All underwent intensive physiotherapy. After 1–2 weeks, 10 out of 13 patients were discharged to a neurorehabilitation center, one to another local hospital and two patients were discharged home to undergo outpatient rehabilitation.

3.3. Postoperative nTMS mapping

nTMS mapping was performed on average 3.8 days (range 1–7 days) after surgery. A positive MEP by nTMS could be elicited in 11 of 13 patients. A detailed listing of the nTMS results for each patient is given in the Table 1.

Of the 11 patients with a positive nTMS MEP, 10 showed a good functional recovery at one month, yielding a positive predictive value of 90.9%. Of the two patients with a negative MEP on nTMS, both showed a poor functional recovery at one month, yielding a negative predictive value of 100%. Of the 10 patients who demonstrated a good outcome, positive MEP by nTMS were elicited in all 10 patients, yielding a sensitivity of 100%. Likewise, of the three

Table 1
Characteristics of the 13 patients included in the study.

ID	Histopathology	Tumor location	Distance CST [mm]	Distance M1 [mm]	Extremity (most affected)	MRCS preOP	1 day postOP	1 week postOP	1 month postOP	io DCS MEP	postOP nTMS	Recovery
1	Anaplastic Glioma	SMA	0	1	leg	5	0	3	5	stable	Present	Yes
2	Metastasis	M1	0	0	leg	4-	3	3	3	loss	Absent	No
3	Glioblastoma	Near IC	0	34	arm	4	0	0–1	1	loss	Absent	No
4	Low Grade Glioma	SMA to VPM	4.27	1.3	arm	5	3	4+	5	stable	Present	Yes
5	Low Grade Glioma	SMA to M1	0	0	leg	4+	2	4	4	stable	Present	Yes
6	Glioblastoma	VPM	8.19	14	arm	5	0	4	4+	loss	Present	Yes
7	Low Grade Glioma	SMA	2.3	2.3	arm	5	0	4-	4+	stable	Present	Yes
8	Glioblastoma	VPM to M1	3.2	0	arm	4+	2	2	4-	irreversible alteration	Present	No
9	Anaplastic Glioma	VPM - Insula	4.1	42	arm	5	0	0	4	irreversible alteration	Present	Yes
10	Anaplastic Glioma	SMA to M1	2.3	0	arm	5	1	4	5	stable	Present	Yes
11	Anaplastic Glioma	SMA	5.1	6.9	arm	5	0	4+	5	stable	Present	Yes
12	Glioblastoma	M1 to Cing	0	0	leg	4	1	2	4	stable	Present	Yes
13	Anaplastic Glioma	SMA to Cing	7.1	23.1	arm	5	2	4	4	stable	Present	Yes

Final histopathology and tumor location with respect to motor eloquence is displayed: M1 = primary motor area; SMA = supplementary motor area; IC = internal capsule; VPM = ventral premotor area, Cing = Cingulum. Column 4 and 5 demonstrate measured distance to corticospinal tract (DTI fibertracking) and M1. Columns 7–10 show neurological evaluation according to Medical Research Council Scale (MRCS) preoperatively (preOP), and postoperatively (postOP) 1 day, 1 week and 1 month after surgery for every most severe extremity affected. The final three columns show the neurophysiological findings of the 13 patients with postoperative motor deficit: io DCS MEP = intraoperative direct cortical stimulated motor evoked potentials via strip electrode, postoperative navigated transcranial magnetic stimulation (nTMS) within 14 days after surgery (average 4 days) and recovery at 1 month after surgery at least to MRCS 4 or above.

patients with a poor outcome, no MEP were elicited by nTMS in two patients, yielding a specifity of 66.7%.

3.4. Correlation of postoperative nTMS and intraoperative IOM

Intraoperative neurophysiological monitoring and mapping was used in all cases.

Direct cortical stimulated MEPs via the strip electrode were stable in eight patients. All of them had positive responses by postoperative nTMS and showed good motor recovery. MEPs were irreversibly altered in two patients and complete loss occurred in three patients (see Table 1). Two out of three patients with DCS MEP loss and one out of two with irreversible DCS MEP alteration presented with significant motor deficit at one month.

None of the two patients with complete loss of intraoperative MEP and absent MEP by nTMS recovered. In case of irreversible alterations or loss of intraoperative MEPs, but positive responses on postoperative nTMS mapping, two out of three patients had a good recovery.

4. Illustrative cases

4.1. Case 1

A 43-year-old male (patient 4) suffered from a first-time focal seizure with secondary generalization. MRI showed a T2-hyperintense lesion located in the superior and medial frontal gyrus corresponding to the supplementary motor area and ventral premotor area (Fig. 1). Clinical examination revealed no focal neurological deficits. The lesion was resected under intraoperative neurophysiological monitoring and continuous subcortical mapping. MEPs elicited by direct cortical stimulation via grid electrode remained stable without any changes. The lowest subcortical mapping threshold was 3 mA. Postoperatively, the patient demonstrated right-sided hemiparesis with pronounced weakness of distal upper extremity (MRCS 3). However, postoperative nTMS mapping confirmed integrity of the corticospinal tract and elicited positive MEPs from the hand at 37% of the generator output (Fig. 1). One month after surgery, the initial postoperative MRCS grade 3 paresis of the right hand had recovered completely and returned to full motor strength.

4.2. Case 2

A 59-year-old male patient (patient 3) presented preoperatively with slight right-sided hemiparesis (MRCS 4). MRI showed a left-sided contrast-enhancing lesion of the insula reaching close to the internal capsule (Fig. 2). Surgery was performed following confirmation of a glioblastoma by biopsy. Intraoperatively during tumor removal, MEPs elicited via the strip electrode were suddenly lost for the arm and irreversibly altered for the leg. Postoperatively, the patient presented with a plegic arm (MRCS 0) and severe paresis of the leg (MRCS 3). Postoperative nTMS MEPs could be elicited from the leg, but not from the arm. One month after surgery, the right arm remained almost plegic (MRCS 1), while the leg had recovered significantly (MRCS 4).

5. Discussion

In supratentorial surgery, intraoperative MEP monitoring indicates the functional integrity of the CST (Sala et al., 2003, Seidel et al., 2013). MEP monitoring is an useful adjunct to cortical and subcortical mapping techniques due to its ability to detect remote vascular injury (Seidel et al., 2013)·(Neuloh et al., 2007, Szelényi et al., 2010). Several series have shown a low risk for permanent change in postoperative motor function as long as intraoperative direct cortical stimulated (DCS) MEPs are preserved without alteration (Deletis et al., 2001a, Sala et al., 2003, Neuloh et al., 2007, Szelényi et al., 2010, Seidel et al., 2013). DCS MEP changes may occur abruptly and are irreversible in around 40% of cases (Neuloh et al., 2007, Seidel et al., 2013). In a recent series in which we analyzed intraoperative DCS MEP changes, we found that following MEP loss, 75% of patients were left with a permanent motor deficit and following irreversible MEP changes (amplitude decre-

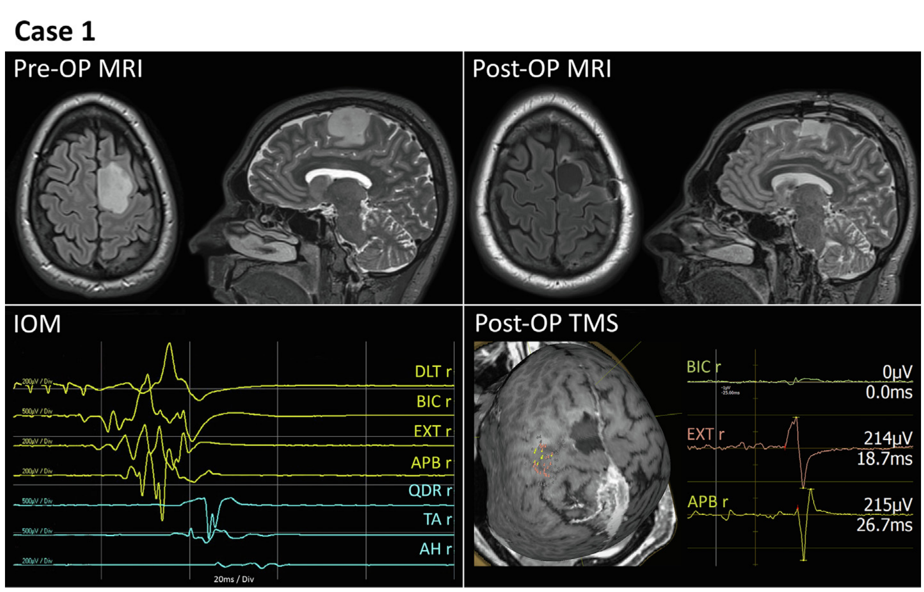

Fig. 1. Upper left-hand corner: preoperative axial fluid-attenuated inversion recovery (FLAIR) and sagittal T2 MRI slice illustrating the tumor location in the superior and medial frontal gyrus (supplementary motor area (SMA) to ventral premotor area (VPM)). Upper right-hand corner: 24-h postoperative axial FLAIR and sagittal T2 MRI slice illustrating complete tumor resection of a low-grade glioma (oligodendroglioma WHO II, LOH 1p/19q). Lower left-hand corner: intraoperative preserved motor evoked potential (MEP) responses for arm, hand (yellow traces) and leg (blue traces) muscles elicited via strip electrode (direct cortical stimulation [DCS] MEP) at the end of tumor resection. Lower right-hand corner: 6 days after tumor surgery nTMS map and EMG recordings performed with positive MEP responses for hand and arm (EXT and APB, purple and yellow dots and lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

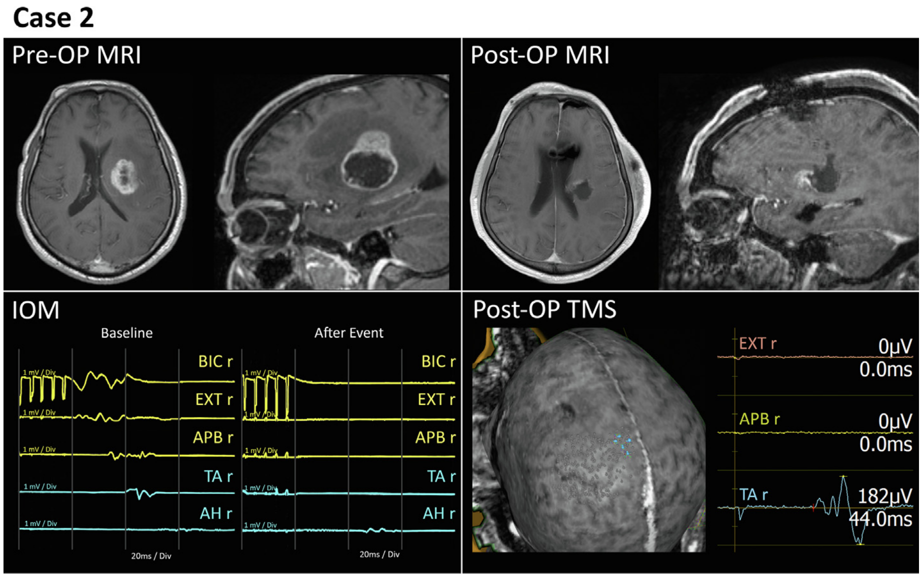

Fig. 2. Upper left-hand corner: preoperative axial and sagittal MRI T1 with gadolinium illustrating the tumor location in the left insula reaching the capsula interna. Upper right-hand corner: 24-h postoperative axial and sagittal MRI T1 with gadolinium illustrating partial tumor resection of a glioblastoma (IDH wild type, TERT mutated, MGMT non-methylated); resection of the anterior part was stopped because of sudden intraoperative motor evoked potential (MEP) loss. Lower left-hand corner: Baseline MEP responses for arm, hand (yellow traces) and leg (blue traces) muscles elicited via strip electrode (direct cortical stimulation [DCS] MEP); MEP responses were suddenly lost and only with high intensity a low amplitude MEP to the leg muscle (AH) could be elicited. Lower right-hand corner: 4 days after tumor surgery – nTMS map and EMG recordings with positive MEP responses for the leg (TA, blue dots and blue lines) but no responses for the arm and hand (EXT and APB, grey dots, purple and yellow lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ment more than 50%, sudden and significant motor threshold increment) 25% had a permanent motor deficit (Seidel et al., 2013). The present series shows similar findings according to our intraoperative monitoring data (see Table 1).

However, permanent neurological deficits may occur after surgery despite extensive intraoperative neurophysiological monitoring and mapping, although at a much lower rate. The uncertainty about whether a limb will recover from paresis is stressful for the patient and the surgeon. Neurological examination may fail to clearly attribute deficits to damage of the primary motor area (M1) or the adjacent supplementary/ventral/dorsal motor area (SMA/VPM/DPM) (Laplane et al., 1977, Zentner et al., 1996, Fontaine et al., 2002), yet the patient will only recover from the latter (Fontaine et al., 2002, Russell et al., 2003). In tumor surgery there might be no isolated lesion to just one classical motor area. More likely, multiple white matter tract connections are involved and for example, SMA and VPM projections are still unresolved (Di Lazzaro et al., 2008, Lemon, 2008, Maier et al., 2013). Furthermore, during removal of a tumor in the posterior part of the superior and medial frontal gyrus, in the depth the corticospinal tract fibers are running in anterior-caudal direction originating from the precentral gyrus travelling to the internal capsule. This is a surgical challenging site, as here the subpial plane is not any more visible and resection into the corticospinal tract might happen. Therefore, combined SMA-primary motor system or VPM-primary motor system lesion deficits might be observed after surgery (Rossi et al., 2018). The patient's quality of life and degree of dependency often influences the choice of adjuvant treatment. Ultimately, guidelines recommend reducing adjuvant treatment of high-grade glioma if a certain threshold of day-to-day independence is not reached by the patient, and new postoperative neurological deficits are known to have a negative impact on overall survival (McGirt et al., 2009).

Non-invasive transcranial magnetic stimulation (TMS) testing could indicate which patients would benefit most from intensive postoperative rehabilitation. In patients with hand palsy due to ischemic stroke, TMS one day after the event has a high predictive value for motor recovery (Rapisarda et al., 1996, Pennisi et al., 1999, Chen et al., 2008). This aspect becomes even more important in the context of adjuvant neuro-oncological treatment in brain tumor patients. In early postoperative TMS studies, Zentner et al. were able to demonstrate that TMS-elicited MEP amplitudes would correlate with stepwise improvement of motor function (Zentner et al., 1996). They illustrated that a patient waking up with postoperative hemiplegia presented no TMS-elicited MEPs, but once the patient gradually recovered his motor strength, MEPs could be elicited with higher and higher amplitudes. TMS was thus shown to have a descriptive value, but was not able to forecast recovery. A limitation of the study might have been the low excitability of the motor cortex additionally influenced by postoperative scalp edema, air collection in the surgical resection cavity and low intensity stimulation. In a single case report, Sala et al. overcame that challenge by applying multi-pulse stimulation with a short train (Sala, 2000). They performed non-navigated TMS one day after surgery in a patient with hemiplegia due to a possible SMA syndrome and recorded TMS-elicited MEP. The patient did recover and had regained full function within a few weeks. Another way to improve the effectiveness in TMS stimulation might be to use navigated TMS, especially as the classical site for the best coil position might be displaced by tumor growth, shift of the primary motor area and the resection cavity (Krieg et al., 2017). To overcome these challenges, Takakura et al. used nTMS and showed that the presence of a positive hand MEP one week after surgery correlated highly with motor recovery (Takakura et al., 2017). So far, postoperative TMS examinations for lower-extremity deficits have been neglected, as MEPs to the leg are more difficult to elicit than MEPs to the hand (Saisanen et al., 2008). In our present series we were able to confirm that in a case when MEP were present in postoperative nTMS performed within 14 days, the patient did recover, at least to MRCS 4 within one month (Fig. 3). Furthermore, we were able to demonstrate this predictive value not only for upper, but also for lower extremity deficits. In the above-described illustrative case (2) of postoperative hemiplegia, the patient (no. 3) presented lower but not upper extremity nTMS-elicited MEP (Fig. 2). This

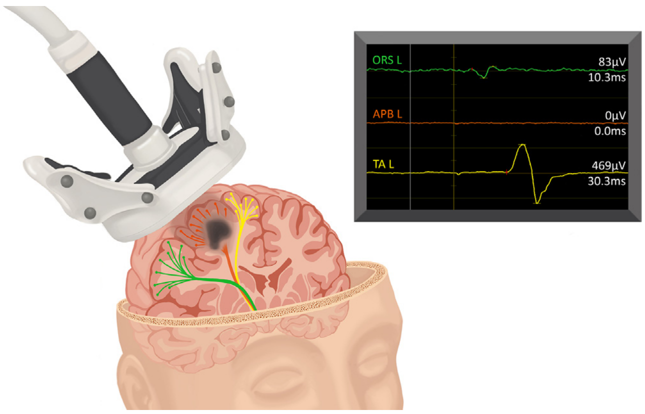

Fig. 3. Schematic illustration of a postoperative navigated transcranial magnetic stimulation examination based on postoperative MRI. The dark area in the white matter illustrates a possible injury to the corticospinal tract (CST) of the hand fibers (red) and a missing MEP response (flat red line). The leg fibers (yellow) and face fibers (green) of the CST are not affected by resection and a positive MEP response can be recorded. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

finding was even more interesting in the context that the motor threshold of the upper extremity is usually much below the lower extremity. Furthermore, fractional-anisotropy-fiber-tracking confirmed an intact CST for the lower extremity, but a lesion of the CST for the upper extremity. The patient did recover leg function within one month but there was no improvement in the hand function. This illustrates the value of focal stimulation with the help of postoperative MRI nTMS.

Intraoperative DCS MEP monitoring at the end of tumor resection and early postoperative nTMS were equal in predicting present or absent long-term motor recovery. In the case of intraoperative DCS MEP loss, as well as in the case of absent postoperative TMS MEP, 75% (DCS) −100% (TMS) of patients did not recover to at least MRCS 4. When intraoperative MEP were stable, all extremities recovered as well as 92% of the extremities with postoperative TMS MEP. The one patient for which TMS MEP were present, but who did not reach our positive endpoint did still recover to MRCS 4- (see Table 1, patient 9), and hence marginally missed our criteria. This patient's postoperative course was complicated by hydrocephalus and ventriculoperitoneal shunt insertion. She deteriorated neurologically and died several months later.

If MEPs were absent in both tests, none of the patients recovered. However in patients with intraoperative DCS MEP alteration or loss, but who had early postoperative TMS positive MEP responses, two out of three patients did recover, which might be an important finding of our study. Patient no. 6 with a Glioblastoma in the Ventral Premotor Area experienced three intraoperative focal seizures. All seizures were easily terminated by irrigation with cold Ringer solution, however after the third seizure no MEP for the arm could be elicited over the strip electrode (baseline MEP with 5 mA). However, MEP for the leg was still present with 17 mA (baseline 9 mA). Displacement of the grid was excluded. The patient presented with an immediate postoperative hemiplegia, however one week after surgery, the leg fully recovered and the arm remained with a moderate deficit. TMS did elicit MEP to both extremities and the patient recovered after one month. A possible cause for the intraoperative MEP loss might have been an increased refractory period/threshold of the primary motor cortex after seizures as well as cold irrigation, which might have changed the excitability of the motor cortex as well. Patient no. 9 underwent tumor removal until a subcortical monopolar short train-mapping threshold of 2 mA was reached. At this point a sudden threshold increment of the via strip electrode elicited MEP for the arm occurred from 6 mA to above 20 mA whereas the MEP for the leg increased from 12 to 20 mA. One week after surgery arm strength was still M0, leg already M3. As correctly predicted by TMS, it took one month that the patient recovered his arm function from M0 to M4. These intraoperative MEP changes might be attributed to reduced excitability of the motor cortex under total intravenous anesthesia (TIVA) at the end of surgery (so called fade phenomena), whereas nTMS was performed in patients who were awake. Excitability of the motor cortex might have been decreased after cold Ringer solution irrigation (patient no. 6) or manipulation close to the CST (patient no. 9). Furthermore, the mechanism of electrical DCS generates MEPs mostly via D-waves (Deletis et al., 2001b, Deletis et al., 2001c) whereas TMS activates the corticospinal tract mostly trans-synaptically via I-waves and therefore assesses primary as well as supportive motor systems (Di Lazzaro et al., 2010, Di Lazzaro et al., 2012). The use of a navigated cone coil instead of a figure-of-eight coil might improve the sensitivity in obtaining postoperative MEP; however, this method was not available in our hospital setting. Anyhow, in our study cohort no patient with intraoperative stable DCS MEP presented with an absent postoperative TMS MEP response, which demonstrates that early postoperative nTMS is practicable and reliable.

The main limitation of our study is the small sample size with just 13 patients. Therefore, statistical analysis might be underpowered. To clearly demonstrate the benefit of postoperative nTMS in predicting long-term motor recovery, larger case series in a prospective multi-center study design would be desirable. Heterogeneity of the included patients with tumors located in primary and secondary motor areas is another important limitation. However, all patients have in common that the tumor location was in average as close as 3 mm to the corticospinal tract and none of them further away than 8 mm (see Table 1). Another aspect to consider is that we did just evaluate pure motor strength and no fine motor skills. Further, as discussed already above, comparing both DCS and TMS, the different mechanism of MEP activation might also influence the results (Di Lazzaro et al., 2008). As TMS elicited MEP are supposed to represent more than pure M1 output, TMS might be slightly beneficial especially when assessing postoperative motor deficits in the included patient series with tumors in primary and secondary motor areas. Again, larger patient series are needed to evaluate this hypothesis.

In summary, we were able to demonstrate the following: (1) If early postoperative nTMS elicited a MEP response, the patient recovered function in this extremity within one month to at least grade 4 on the MRCS scale. (2) If MEP could not be elicited with 70–100% of maximal TMS machine output, none of the affected extremities did recover significantly. (3) Intraoperative DCS MEP monitoring at the end of tumor resection and early postoperative nTMS were of equal reliability in predicting the likelihood of long-term motor recovery. However, in cases of intraoperative MEP alteration or signal loss, but a positive postoperative nTMS mapping response, two out of three patients demonstrated a good motor recovery. Therefore, postoperative nTMS might guide postoperative treatment strategies and support intensive postoperative rehabilitation in selected cases. nTMS is a non-invasive easily assessable examination, which is even possible in an outpatient setting and might be repeated several times for follow-up examinations.

6. Conclusion

Early postoperative nTMS may reliably predict long-term motor recovery of patients suffering from severe motor deficits immediately after resection of tumors located in motor eloquent areas. In the case of intraoperative alterations of MEP monitoring, early postoperative nTMS may clarify the potential of rehabilitation for motor recovery.

In patients, who underwent surgery involving primary motor cortex and associative motor areas, nTMS carries the potential to asses more than just primary motor cortex output. In long-term, TMS might indicate which patients benefit most from intense rehabilitation and TMS may even open possibilities for new treatment paradigms in rehabilitation.

However, this study describes a series of 13 patients and larger case series are needed to validate this statement. We suggest further multi-center prospective studies, which prove the benefit of postoperative nTMS in predicting long-term motor recovery.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. All authors have approved the final article.

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