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Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations

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Background. Neurological and oncological outcomes of motor eloquent brain-tumor patients depend upon the ability to localize functional areas and the respective proposed therapy. We set out to determine whether the use of navigated transcranial magnetic stimulation (nTMS) had an impact on treatment and outcome in patients with brain tumors in motor eloquent locations.

Methods. We enrolled 250 consecutive patients and compared their functional and oncological outcomes to a matched pre-nTMS control group ($n = 115$).

Results. nTMS mapping results disproved suspected involvement of primary motor cortex in 25.1% of cases, expanded surgical indication in 14.8%, and led to planning of more extensive resection in 35.2% of cases and more restrictive resection in 3.5%. In comparison with the control group, the rate of gross total resections increased significantly from 42% to 59% ($P < .05$). Progression-free-survival for low grade glioma was significantly better in the nTMS group at 22.4 months than in control group at 15.4 months ($P < .05$). Integration of nTMS led to a nonsignificant change of postoperative deficits from 8.5% in the control group to 6.1% in the nTMS group.

Conclusions. nTMS provides crucial data for preoperative planning and surgical resection of tumors involving essential motor areas. Expanding surgical indications and extent of resection based on nTMS enables more patients to undergo surgery and might lead to better neurological outcomes and higher survival rates in brain tumor patients. The impact of this study should go far beyond the neurosurgical community because it could fundamentally improve treatment and outcome, and its results will likely change clinical practice.

Keywords: clinical and oncological outcome, diffusion tensor imaging, intraoperative monitoring, motor eloquent brain tumors, navigated transcranial magnetic stimulation.

The recommended first-line treatment for most brain tumors is undelayed aggressive resection.[1,2] Since preoperative risk assessment on the basis of standard anatomical imaging alone is often insufficient, noninvasive identification and visualization of eloquent areas in the preoperative work-up is becoming increasingly important in brain tumor surgery.[3] In glioma patients, a presumed eloquent location has been identified as a key variable influencing the treatment strategy,[4,5] regardless of the fact that intraoperative stimulation mapping enables extensive resection of tumors in eloquent locations.[6,7]

Navigated transcranial magnetic stimulation (nTMS) has been recently established as a reliable tool for distinguishing resectable from nonresectable cortical tissue in the motor areas.[8,9] It has also been reported that the addition of nTMS to the presurgical work-up can lead to more radical resections.[10,11]

With this study, we set out to investigate whether nTMS data have an impact on the clinical outcome for patients with tumors in presumed motor eloquent locations.

Patients and Methods

Ethics

The study proposal was approved by the Ethics Commission of the Charité University Hospital (reference #EA4/007/06). The patients provided written informed consent for all medical evaluations and treatments.

Participants

The prospective nTMS group included all patients evaluated for surgery for a tumor in a motor eloquent location between May 2007 and October 2012. "Motor eloquent" was defined as suspected invasion of the precentral gyrus (Fig. 3A) or compression without identifiable sulcus between tumor and precentral gyrus and/or suspected invasion of the corticospinal tract, as evaluated by the neurosurgeon who counseled the patient initially (Fig. 2). The exclusion criteria were frequent generalized

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seizures (more than 1/week) and existence of cranial implants. As a control group, we retrospectively identified all patients who met the same in- and exclusion criteria from January 2005 through April 2007.

Participant sociodemographic and medical variables as well as nTMS mapping results were archived in a purpose-made database for later analysis. Every participant was evaluated on preoperative day 1, postoperative day 7, and at follow-up after 3 and 6 months.

Navigated Transcranial Magnetic Stimulation

All participants underwent brain mapping with nTMS (eXimia; Nexstim), as previously described.[8] Briefly, the eXimia system uses a high-precision, figure-of-eight stimulation coil, combined with neuronavigation and analytic software to deliver biphasic magnetic stimulation to spots on the motor cortex. This stimulation may then result in muscle output, which is recorded on the system's integrated electromyogram using surface electrodes (Neuroline 720; Ambu;) attached to the abductor pollicis brevis, the first digital interosseus, the adductor digiti minimi, and the tibial anterior muscles. The participants were instructed to relax with their eyes open (Fig. 1). Stimulation was always performed on both the affected and the healthy hemisphere. In addition, motor tracts were visualized using the cortical nTMS spots outlining the primary motor cortex as seed points (Brainlab iPlan 2.0). In principle, tractography was performed in an anterograde direction, according to the principal eigenvector' direction for each voxel in the region of interest, as previously described.[12] The resulting fibers were visualized at 75% of the individual fractional anisotropy threshold, as previously described in detail (Fig. 3B).[13] Measurement for minimal distances between lesions and nTMS-based fiber tracts were performed in the respective transversal plain of the surgical planning software (iPlan 2.0, Brainlab).

Integration into Surgical Planning

The respective surgeons were provided with patient data including history, neurological status, and magnetic resonance imaging (MRI) scans. After definition of indication, strategy, approach, and planned extent of resection, the nTMS results were presented to the surgeon by exporting the nTMS-derived motor map and fiber tracking into a navigation program (iPlan; BrainLab). The surgeon then designed the surgical plan again and evaluated the influence of nTMS results on the surgical plan using a 0-3 descriptive categorical ranking questionnaire: (0) no change in the surgical plan; (i) nTMS led to a modification of the operative access pathway and/or size of craniotomy; (ii) nTMS led to a change in the planned extent of resection; and (iii) nTMS changed the surgical indication (from no surgery/biopsy to resective surgery or vice versa). In addition, the necessity of using intraoperative stimulation mapping was assessed before and after presentation of nTMS results.

Intraoperative Stimulation Mapping

The nTMS outline of the primary motor cortex and the tractography results were projected into the microscopic view (Fig. 3C). Peritumoral mapping was performed freehand in 5 mm steps. Intraoperative stimulation mapping details under general anesthesia have been described previously.[14] Briefly, monopolar, anodal trains of 5 square-wave pulses (0.3 ms, 400 Hz) were used. The stimulation intensity was increased in 1 mA steps until a muscle action potential could be recorded or an upper limit of 25 mA was reached for cortical mapping and 10 mA for subcortical mapping. Motor responses were recorded using subdermal needle-electrodes placed 5 to 10 mm apart over the same hand and leg muscles recorded during nTMS. Muscle-evoked potential responses at 2 mA were defined as the stop signal during subcortical resection. The surgeon's subjective assessment of the usefulness of nTMS data implementation was documented as well as the influence of the nTMS data on the planned approach and size of the craniotomy.

Extent of Resection

Tumor dimensions were circumscribed manually for low-grade tumors on the basis of fluid-attenuated inversion recovery (FLAIR) images for all other histologies on gadolinium-enhanced T1-weighted images using neuronavigation software (Brainlab iPlan 2.0). For evaluation of extent of resection, we compared preoperative MRI scans with MRI scans obtained within 48 hours after surgery. Again, tumor dimensions were defined as described above, and 4 groups were assessed based on a common classification system:[15] "gross total resection" when no contrast enhancing was detected in the subtracted images or FLAIR volume was eliminated in low-grade glioma, respectively, "subtotal resection" in case of $<$10 mL residue, "partial resection" in case of more than 10 mL residue, and "biopsy".

Functional Outcome and Quality of Life

The motor function, using the British Medical Research Council (BMRC) scale and the Karnofsky performance score (KPS), were assessed by the attending physician preoperatively, on postoperative day 7, and after 3 months.

Progression-free Survival

All participants were followed up at 3-month intervals. The assessment of tumor progression was derived from FLAIR-weighted images in low-grade glioma and from contrast-enhanced MRI scans in all other cases.

Statistical Analysis

Descriptive statistics were used to characterize the participants' samples and outcome variables. The data were close enough to a normal distribution to calculate means. Pearson's correlation coefficients, together with chi-square-testing, were calculated to examine the relation between nTMS group and control group variables.

Results

Participant Sample

There were 250 participants included in the nTMS group. The median age was 54 years (range, 19 y–82 y). One-hundred forty-eight (59%) participants had a motor deficit, and 139 (56%) were treated

for symptomatic epilepsy. There were 128 glioma participants (WHO grade II–IV), 85 with metastases and 37 with other lesions. The pre-nTMS group comprised 115 participants who were well-matched for all key variables (Table 1).

Validity of nTMS Mapping

Brain mapping with nTMS did not evoke any seizures or other side effects. Five participants (2%) complained about transient headache. The mean (range) mapping time was 15.2 minutes (range, 6min–29 min).

In 165 cases, intraoperative stimulation mapping was performed. The depiction of the primary motor cortex by nTMS was confirmed intraoperatively in all cases. Navigated intraoperative stimulation mapping was performed in 82 cases. The mean (range) distance between nTMS and intraoperative stimulation mapping hot spots for abductor pollicis brevis muscle was 6.2 mm (range, 0.4 mm –14.8 mm). No statistical difference was observed regarding accuracy when comparing the glioma cases ($n = 57$) with other histologies ($n = 25$).

nTMS-based Fiber Tracking

Data were available for analysis from 205 participants. Fractional anisotropy threshold values ranged from 0.07 to 0.38 (median, 0.18) for the affected hemisphere and from 0.12 to 0.40 (median, 0.32) on the contralateral hemisphere ($P < .001$). In all cases, refined fiber tracking at 75% fractional anisotropy threshold was primarily successful without need for any post-processing corrections.

Impact of nTMS: Surgical Planning

Surgical indication and planned extent of resection were affected by the nTMS results. The planned extent of resection was increased in 81 (32.4%) category "0" cases, 53 (21.2%) category "1" cases, and 64 (25.6%) category "2" cases, while more restrictive resections were planned in 9 (3.6%) cases. Changes in planned resective surgery were made in 40 (16%) category "3" cases, and planned surgery was changed to biopsy/no surgery in 3 (1.2%) cases. Overall, the conversion rate was 68% (37/54) (Figs. 2 and 4).

Impact of nTMS: Intraoperative Stimulation Performance

The cortical nTMS information facilitated identification of the primary motor cortex in all 165 intraoperative stimulation mapping cases. Phase reversal was waived in 95% of these cases, which led to smaller craniotomies in 17.5%. Intraoperative stimulation during surgery did not lead to modification of the planned approach pathway or the planned extent of resection with regard to total versus partial resection in any of the participants. Guidance of the subcortical stimulation probe by nTMS-based tractography was regarded as beneficial by facilitating identification of tracts in 58% of all cases.

Impact of nTMS: Motor and Functional Outcome

The addition of nTMS did not lead to a significant change of new postoperative deficits, as can be seen in Table 1. In comparison

Table 1. Demographic and clinical characteristics of the 365 participants

nTMS	Period	*n*	Sex and Age (Range)	Histologies (according to WHO Tumor Grade)	Tumor Location	Functional Outcome all Histologies		Motor Outcome all Histologies (Glioma Only)			Extent of Resection Glioma Only	Progression-Free Survival Glioma Only
						On Admission	3 Moths. Postop	On Admission	3 Months. Postop		No. (%)	All Glioma/*Low Grade Glioma*
No	1/2005–4/2007	115	67 Men 48 Woman 53 years (23–81)	*Glioma III/IV 37 (32%)* *Glioma II 18 (16%)* Metastases 40 (35%) Other[1] 20 (17%)	Presumed involvement[3]: Motor cortex 32 (28%) Corticospinal tract 22 (19%) Both 61 (53%)	BMRC 4.2 (1–5) KPS 92 (50–100)	BMRC 4.0 (2–5) KPS 91 (60–100)	Motor deficit 55% (47%)	New deficits 8.5% (9.5%)		Gross total 23/55 (*41.8%*)* Subtotal 6/55 (*10.9%*) Partial 12/55 (*21.2%*) Biopsy 14/55 (*25.4%*)*	12.4 (3–38)/ *15.4 (6–42)**
Yes	5/2007–10/2012	250	139 Men 111 Woman 54 years (19–82)	*Glioma III/IV 90 (36%)* *Glioma II 38 (15%)* Metastases 85 (34%) Other[2] 37 (15%)	Presumed involvement: Motor cortex 88 (35%) Corticospinal tract 35 (14%) Both 127 (51%)	BMRC 4.1 (1–5) KPS 91 (50–100)	BMRC 4.3 (2–5) KPS 92 (60–100)	Motor deficit 59% (51%)	New deficits 6.1% (7.5%)		Gross total 75/128 (*58.6%*)* Subtotal 12/128 (*9.4%*) Partial 23/128 (*18.0%*) Biopsy 18/128 (*14.1%*)*	15.5 (3–51)/ *22.4 (11–50)**

*$P < 0.05$.

with the control group, (8.5% all tumors/9.5% glioma only) the rate of new postoperative deficits was slightly lower in the nTMS group (6.1%/7.5%, respectively) but did not yield significance. The quality of life, based on 3-month postsurgical KPS assessment, did not demonstrate significant statistical change when the 2 groups were compared (nTMS group: 16.5% improved, 4% worsened, 79.5% unchanged; control group: 12.5% improved, 7.5% worsened, 80% unchanged).

Impact of nTMS: Extent of Resection (Glioma Only)

In the nTMS group, gross total resection was achieved in 75 of 128 (58.6%) participants according to postoperative MR imaging, whereas gross total resection was achieved in 23 of 55 (41.8%) participants in the control group ($P < .05$). Intraoperative stimulation mapping was always used in both groups when open surgery was performed. The incidence of biopsies was significantly higher ($P < .05$) in the control group (25.4%) than in the nTMS group (14.1%).

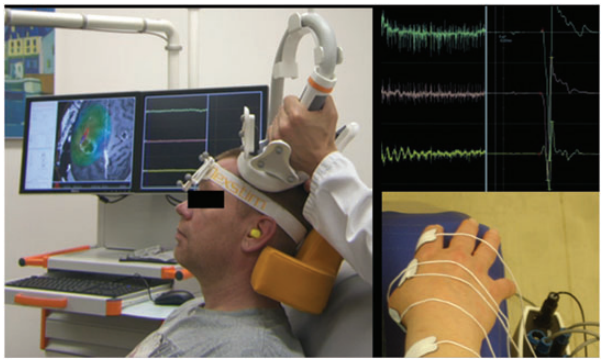

Fig. 1. Photographs showing the nTMS system during stimulation. Motor responses are evoked by magnetic stimulation by a coil placed on the patient's head and recorded by surface electrodes placed on the respective muscles. A 3D-reconstruction of the brain with coil localization is shown on the monitor.

Impact of nTMS: Progression-free Survival (Glioma Only)

The mean (range) follow-up in the nTMS group was 22.5 (range, 6–62) months and 25.4 (range, 9–57) months in the control group. The mean (range) overall progression-free survival was 15.5 (range, 3–51) months in the nTMS group and 12.4 (range, 3–38) months in the control group . For the subgroup of low-grade gliomas, progression-free survival was 22.4 (range, 11–50) months in the nTMS group and 15.4 (range, 6–42) months in the control group ($P < .05$). However, there was no statistical difference between the groups in overall survival. With regard to cofactors that might influence outcome data, no significant difference was found in adjuvant chemotherapy and/or radiation therapy treatment between the 2 groups.

Impact of nTMS: Risk Stratification

The nTMS results disproved the assumed involvement of the primary motor cortex in 54 of 215 cases (25.1%), and involvement of the corticospinal tract alone was suspected in 35 participants. Analysis of all tractography cases ($n = 205$) revealed that no surgical morbidity occurred if the minimal distance between the tumor and the corticospinal tract exceeded 10 mm (Fig. 4).

Discussion

Background

The indication for any surgical procedure essentially consists of weighing and balancing the potential harm from the disease

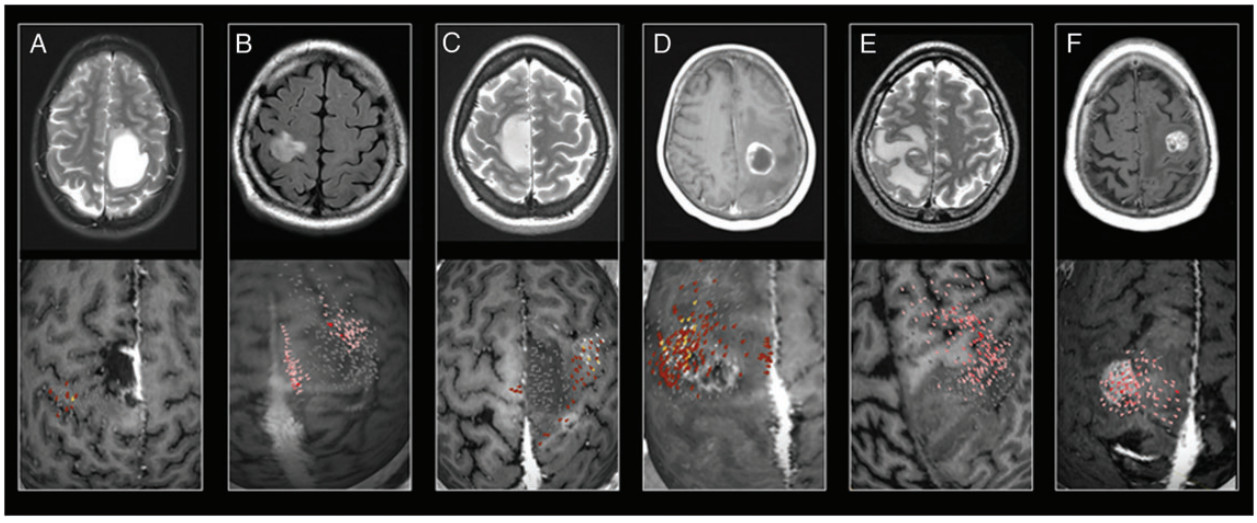

Fig. 2. Six exemplary cases with tumors involving the motor cortex that were initially evaluated as being ineligible for surgery due to suspected motor eloquent location. nTMS analysis resulted in conversion to surgery for cases A–E. In case F, motor involvement was verified by nTMS, and the patient was scheduled for biopsy. Colored pins depict the primary motor cortex for hand and leg representation, respectively. Grey pins depict nonmotor functional tissue. For motor-positive sites, color-coding follows the principle of "the brighter the color, the larger the motor response." White pins show maximal responses.

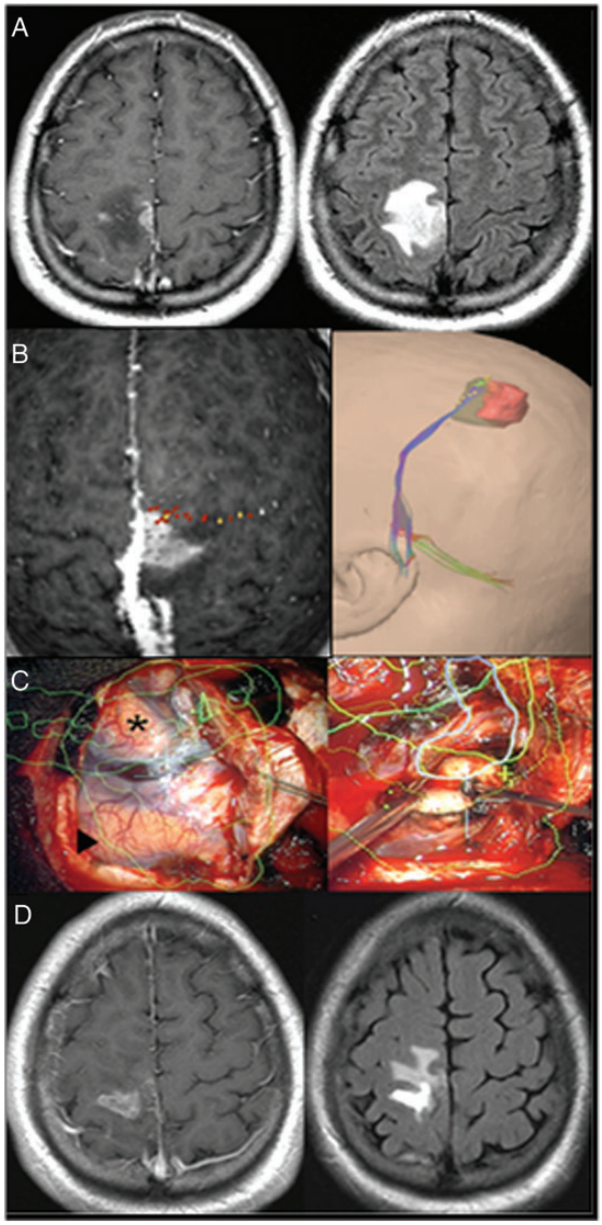

Fig. 3. The patient presented with seizures of the left leg and no motor deficit. A biopsy was initially planned due to the presumed involvement of the primary motor cortex. After nTMS mapping and nTMS-based fiber tracking, the plan was changed to resection of the malignant part of the tumor. (A) Preoperative MR scans. (A, left) contrast enhancement in T1, suggesting involvement of the primary motor cortex; (A, right) FLAIR image. (B, left) nTMS result with colored pins depicting the primary motor cortex and grey pins depicting nonmotor functional tissue. The examination demonstrates postcentral localization of the contrast-enhancing part of the tumor; (right) result of nTMS-based tractography. Tumor dimensions colored in red and area of altered FLAIR signal in transparent green. Note that the nTMS pins outlining the primary motor cortex and the nTMS-based tractography are within the tumor infiltration zone (FLAIR area) but spare the supposedly malignant part of the tumor. (C, left) intraoperative view of the primary motor cortex overlaid with the nTMS results (*). Note the exact overlay of the anatomy by the virtual image, which is a prerequisite for relying on the preoperative data. The tumor in its maximal diameter is outlined by the dotted yellow line (►). (C, right) identification of corticospinal tract with the monopolar-stimulation probe guided by nTMS-based tracts (light blue line) injected into the microscopic view. (D, left) the postoperative contrast-enhanced T1 image demonstrates removal of the contrast-enhancing part of the tumor. (D, right) the area of altered FLAIR signal involving the functional primary motor cortex has been spared.

against the risk generated by the intervention itself. In the existence of brain tumors located in motor eloquent areas, this dilemma translates into the question of the benefits we create for the patient in terms of extended survival, preservation or restoration of function and mobility and, the consequent maintained quality of life versus the risk of new neurological deficits at the same time.

Discussing this balance with the patient and planning the procedure can be difficult if the surgical team does not have patient-specific knowledge of the spatial relationship between the tumor and motor areas. The functional organization shows major variations between individuals, even in physiologic conditions. Space-occupying tumors render landmark-based localization of functional areas prone to inaccuracy because cortical structures may be shifted or infiltrated, leading to a disruption of anatomico-functional structures. Functional reorganization of the infiltrated areas can also occur.[16,17] Hence, existing approaches might insufficiently reflect the complex network of motor cortical organization and lead to improper restraint in surgical indication, high morbidity, and/or decreased chance of progression free-survival.

In a recently published study, the authors claimed that patients with motor-related tumors who underwent nTMS mapping presurgically had better surgical and functional outcomes than a historic control group before the introduction of nTMS.[18] We conducted a study to investigate whether these results could be confirmed on a larger patient cohort and to analyze whether the additional implementation of nTMS led to a survival benefit in glioma patients.

Functional Imaging and TMS Validity

Specialists can identify the motor cortex in tumor patients using imaging technologies that rely on recording changes in brain activity in response to the patient's performance of a task.[19,20] These technologies require a lot of time and expertise, however, and can still leave uncertainty about the exact border between the tumor and the motor cortex because voluntary motor tasks do not necessarily activate primary motor areas alone, and brain lesions might result in a disruption of neurovascular coupling. This may lead to an inaccurate representation of motor function in the vicinity of space-occupying lesions.[21,22] By contrast, nTMS can localize the borders of functional motor cortex by focal electrical stimulation of the cortex, allowing for detailed delineation of resectable versus nonresectable cortical tissue.[8–10,23–27] The findings of these studies on 138 participants are confirmed by the current study in which the nTMS results were confirmed by intraoperative stimulation mapping in 165 participants. In addition to its spatial accuracy, recent studies have shown that nTMS results are also consistent over time, regardless of the experience of the person performing the procedure.[28,29]

Risk stratification based on nTMS cartography	
Suspected involvement of motor cortex in 215/250 (86%) cases	
True eloquent 161 (74.9%)	False eloquent 54/215 (25.1%)
Net change biopsy/no surgery to surgery 37/54 → Conversion rate 68.5%	

Risk stratification based on nTMS tractography	
Measuring minimal tumor-corticospinal tract distance	Resulting in mean (range) values of 5.7mm (0-22mm)
→ No new neurological deficit after surgery when tumor-tract-distance ≥ 11mm	

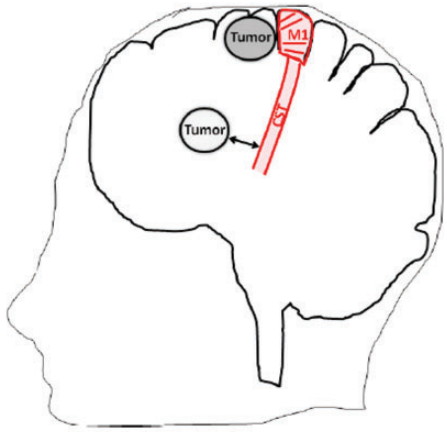

Fig. 4. Risk stratification based on nTMS cartography and tractography for tumors suspected to involve the primary motor cortex and/or the corticospinal tract. Measurement for minimal tumor-corticospinal tract distance was performed in the respective transversal plain of the surgical planning software.

Impact of nTMS on Surgical Planning

For tumors in eloquent locations, intraoperative stimulation mapping helps to increase the extent of resection, while at the same time reducing the incidence of new neurological deficits inflicted by surgery.[3,6] Consequently, intraoperative stimulation mapping has to be regarded as mandatory when operating on tumors in eloquent locations. Yet, it has been repeatedly shown that despite the consensus about the benefit of early resection a presumed eloquent location regularly leads to a more conservative treatment. The resulting defensive strategy is one key factor influencing the surgical outcome already preoperatively.[4,5] In this study, preoperative nTMS mapping results disproved the suspected involvement of the primary motor cortex in 25.1% of cases. Planned biopsy/no surgery was changed to resective surgery after nTMS mapping in 16% of cases, and planned surgery was changed to biopsy/no surgery in 1.2% of cases, resulting in a net increase of 37 patients who were eligible for surgery (Fig. 4). In comparison with the control group, planning for more extensive surgery resulted in more frequent gross total resections and longer progression-free intervals. Functional outcomes were also better, although this change was not statistically significant.

Impact of nTMS on Morbidity and Extent of Resection

We observed an overall rate of new or increased motor deficits of 6.1% for nonglioma and 7.5% for glioma participants in the nTMS group at the 3-month follow-up. This morbidity profile is in accordance with results of other current studies that showed a 2%–13% rate of neurological deterioration 3 months after surgery for glioma.[3,6,30] Since comparison of outcome data between institutions is biased by varying inclusion and treatment algorithms, we used an in-house control group of cases that were treated before we introduced TMS into our clinical routine.[30] The 2 groups were well matched in their clinical variables and, most importantly, the surgical teams and their expertise in intraoperative stimulation mapping were similar in both groups. Therefore it can be concluded from our findings that nTMS was crucial in achieving more total resections in the nTMS group than in the control group (60% vs 42%) at a stable morbidity rate. Especially in low-grade glioma patients, which are tended to be treated more restrainedly, it could be shown that the integration of nTMS enables early aggressive resection without increasing neurological morbidity.

Impact of nTMS on Progression-free-Survival

In glioma patients, it has been shown that the extent of resection correlates independently with patient survival.[2,30,31] Consequently in our 2 patient groups, progression-free-survival in the nTMS group (15.5 months) was significantly longer than in the control group (12.4 months). Together with the facts that more radical resections did not result in a higher rate of new neurological deficits and that progression-free-survival in low-grade glioma was significantly higher, we can conclude that surgical and oncological benefit was not outweighed by neurological compromise.

Preoperative Risk Stratification

We could show that no new neurological deficits occurred whenever the primary motor cortex was not involved by the tumor and the tumor-tract-distance exceeded 10 mm. With all caution towards the interpretation of fiber tracking, these tumors can thus be regarded as nonmotor functional.

Limitations of the Study

The main limitation of the study, in respect to its conclusions about the impact of nTMS on decision-making and treatment outcome, is the lack of a concurrent, ideally randomized control group. The design of the study does not allow ruling out

subjective factors in terms of evaluating the impact on decision-making and accounting for general changes in treatment strategies (eg, the adoption of a more aggressive treatment strategy, especially in low-grade glioma patients). Nevertheless, a randomized study would deny many patients the best available treatment and, in our opinion, would contradict the ethical commitment of a physician.

Conclusions

The integration of navigated transcranial magnetic stimulation into the surgical workflow crucially improves preoperative planning, patient counseling, and surgical procedures and leads to longer progression-free survival rates and better neurological outcomes by expanding the indications and extent of resection. Not only may this study open the door to surgery for many patients who are currently denied surgical treatment, it may also bring about improvements in the surgical procedures, leading to increased progression-free survival and decreased morbidity rates. Because nTMS is becoming more widely available, we believe the results of this study should be applied to the neurological and neurosurgical community as a whole. Thus, the introduction of nTMS could soon be regarded as landmark advancement in the treatment of brain tumor patients and will likely change general clinical practice.

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