Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation

Clinical article

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Object. Preserving motor function is a major challenge in surgery for intraaxial brain tumors. Navigation systems are unreliable in predicting the location of the corticospinal tracts (CSTs) because of brain shift and the inability of current intraoperative systems to produce reliable diffusion tensor imaging data. The authors describe their experience with elaborate neurophysiological assessment and tractography-based navigation, corrected in real time by 3D intraoperative ultrasonography (IOUS) to identify motor pathways during subcortical tumor resection.

Methods. A retrospective analysis was conducted in 55 patients undergoing resection of tumors located within or in proximity to the CSTs at the authors’ institution between November 2007 and June 2009. Corticospinal tract tractography was coregistered to surgical navigation-derived images in 42 patients. Direct cortical-stimulated motor evoked potentials (dcMEPs) and subcortical-stimulated MEPs (scrtMEPs) were recorded intraoperatively to assess function and estimate the distance from the CSTs. Intraoperative ultrasonography updated the navigation imaging and estimated resection proximity to the CSTs. Preoperative clinical motor function was compared with postoperative outcome at several time points and correlated with incidences of intraoperative dcMEP alarm and low scrtMEP values.

Results. The threshold level needed to elicit scrtMEPs was plotted against the distance to the CSTs based on diffusion tensor imaging tractography after brain shift compensation with 3D IOUS, generating a trend line that demonstrated a linear order between these variables, and a relationship of 0.97 mA for every 1 mm of brain tissue distance from the CSTs. Clinically, 39 (71%) of 55 patients had no postoperative deficits, and 9 of the remaining 16 improved to baseline function within 1 month. Seven patients had varying degrees of permanent motor deficits. Subcortical stimulation was applied in 45 of the procedures. The status of 32 patients did not deteriorate postoperatively (stable or improved motor status): 27 of them (84%) displayed minimum scrtMEP thresholds > 7 mA. Six patients who experienced postoperative deterioration quickly recovered (within 5 days) and displayed minimum scrtMEP thresholds > 6.8 mA. Five of the 7 patients who had late (> 5 days postoperatively) or no recovery had minimal scrtMEP thresholds < 3 mA. An scrtMEP threshold of 3 mA was found to be the cutoff point below which irreversible disruption of CST integrity may be anticipated (sensitivity 83%, specificity 95%).

Conclusions. Combining elaborate neurophysiological assessment, tractography-based neuronavigation, and updated IOUS images provided accurate localization of the CSTs and enabled the safe resection of tumors approximating these tracts. This is the first attempt to evaluate the distance from the CSTs using the threshold of subcortical monopolar stimulation with real-time IOUS for the correction of brain shift. The linear correlation between the distance to the CSTs and the threshold of subcortical stimulation producing a motor response provides an intraoperative technique to better preserve motor function.

(DOI: 10.3171/2010.8.JNS10639)

Key Words • subcortical mapping • corticospinal tract • ultrasonography-based neuronavigation • motor evoked potential • brain tumor • pyramidal tract

Abbreviations used in this paper: CST = corticospinal tract; dcMEP = direct cortical-stimulated motor evoked potential; DT = diffusion tensor; FA = fractional anisotropy; IOUS = intraoperative ultrasonography; ROI = region of interest; scrtMEP = subcortical-stimulated MEP; SPGR = spoiled gradient echo; SSEP = somatosensory evoked potential.

* Dr. Nossek and Mr. Korn contributed equally to this work.
variety of methods in modern neurosurgery designed to achieve that goal of maximal and safe tumor resection, including the use of preoperative diagnostic and functional imaging, tractography, intraoperative navigation, and intraoperative neurophysiological recordings in both anesthetized and awake patients.1,2,4,11,15

Intraoperative neurophysiological monitoring and mapping has gained popularity in recent years for use during surgical procedures adjacent to the motor cortex and its subcortical components.2,4,6,11,15,16 Electrical stimulation of white matter at the resection cavity has been described as a technique for assessing proximity to the subcortical CSTs and to determine whether resection should be halted in an effort to minimize CST injury.3,4,17,18 However, that technique involves binary interpretation—that is, the presence or absence of a motor response to the delivered subcortical stimulus at a constant intensity—and cannot quantify the actual distance between the stimulated point and the CST. There have been recent attempts to estimate that distance,9,14,18 but the accuracy of measurement was hampered by inherent intraoperative brain shift. Solving the brain shift problem by assessing the stimulation points on postoperative MR imaging13 has inherent shortcomings. Another technique described by Ozawa and colleagues20,22 involved the use of intraoperative diffusion weighted MR imaging to estimate the extent of brain shift; however, this technique was less accurate in localizing the CSTs.

In this paper we describe our findings when we used preoperative MR imaging/DT imaging, intraoperative subcortical stimulation (scrtMEPs) in conjunction with direct cortical stimulation (dcMEPs), and real-time intraoperative imaging to compensate for brain shift in an attempt to quantify the relationship between scrtMEP stimulation thresholds and distances from the CSTs. Clinically, the electrophysiological data were correlated to the postoperative functional outcome of the patients to generate methodological recommendations that would help the surgical team achieve maximal tumor resection without injury to the CSTs.

Methods

This retrospective study based on prospectively collected data was approved by the Tel Aviv Medical Center Institutional Review Board committee (IRB approval number 0161–09).

Study Participants

Fifty-five patients (35 males, 20 females) with a mean age of 46.3 years (range 18–81 years) underwent resection of a supratentorial lesion located within or 2 cm from the CST as determined by preoperative MR imaging. The enrolled patients underwent surgery during a period of 19 months (November 2007–June 2009). One patient underwent 2 procedures, and the data for each were evaluated separately. The tumor locations and pathological diagnoses are listed in Tables 1 and 2. Twenty-eight patients (51%) had no preoperative motor deficits, whereas 27 (49%) had various degrees of preoperative motor deficits (Table 3). Preoperative Karnofsky Performance Scale scores ranging from 30 to 100 were documented for each patient: 41 patients scored within 80–100, 13 within 50–70, and 1 had a score of 30. All 55 patients underwent preoperative MR imaging; 42 patients underwent preoperative DT imaging of the CSTs and their data were used for tractography-based neuronavigation. Eighteen patients also underwent preoperative functional MR imaging assessment for motor and language cortex mapping. Thirty-four patients (62%) had a right-sided lesion. Thirty-five patients (64%) underwent awake craniotomy. Gross-total resection (>95%) of the lesion was achieved in 39 patients (71%), and subtotal resection in the remaining 16 (29%).

Pathological Analysis

Thirty lesions were diagnosed as high-grade gliomas, 16 as low-grade gliomas, 1 as radiation necrosis, 3 as cavernous hemangiomas, 3 as metastatic lesions, and 2 cases involved resection of nonlesional epileptic foci (Table 2). Overall, the most frequently encountered pathology in this population was glioblastoma multiforme (40% of the cases). Grade II oligodendroglioma (62%) constituted the highest incidence of low-grade glioma in our patient series.

Radiological Data

Magnetic resonance imaging was performed on a 3.0-T scanner (GE Sigma EXCITE HD). The protocol included conventional MR imaging: T1, T2, and FLAIR sequences, DT imaging, and contrast-enhanced T1 sequences. Diffusion tensor images were acquired with b values of 0 and 1000 seconds/mm² at 19 noncollinear gradient directions. Additional parameters included axial slices 3 mm in thickness with no gap covering the entire brain (field of view 200) and in-plane resolution of 0.7813 × 0.7813 mm². Diffusion tensor analysis was performed using MR imaging Studio software (DTI Studio, Version 2.4.01, October 2007). In the DT imaging analysis, the diffusion tensor (that is, a 3 × 3 matrix) was calculated

<table>
<thead>
<tr>
<th>TABLE 1: Lesion location in 55 patients</th>
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<tbody>
<tr>
<td>Location</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>frontal lobe</td>
</tr>
<tr>
<td>parietal lobe</td>
</tr>
<tr>
<td>temporal lobe</td>
</tr>
<tr>
<td>insular cortex</td>
</tr>
<tr>
<td>&gt;1 lobe</td>
</tr>
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</table>

<table>
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<tr>
<th>TABLE 2: Pathological diagnoses</th>
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<tbody>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>high-grade glioma</td>
</tr>
<tr>
<td>low-grade glioma</td>
</tr>
<tr>
<td>radiation necrosis</td>
</tr>
<tr>
<td>cavernous hemangioma</td>
</tr>
<tr>
<td>metastasis</td>
</tr>
<tr>
<td>epileptic focus</td>
</tr>
<tr>
<td>No. of Specimens</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>2</td>
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</tbody>
</table>
with a multivariate linear fitting algorithm for each voxel. The tensor in each voxel was spectrally decomposed to obtain its eigen values and eigen vectors, and the fiber direction at each voxel was assumed to be the eigen vector corresponding to the tensor’s largest eigen value. This vector was color-coded (blue for superior-inferior, red for left-right, and green for anterior-posterior).

A streamline fiber tracking method was applied using DTI Studio software. A fiber assignment by continuous tracking (FACT) algorithm and a brute-force reconstruction approach were used. For the tracking of white matter fibers, the multiple ROIs method was applied, in which ROI 1 = unilateral ventral pons, ROI 2 = posterior limb of the internal capsule, and ROI 3 = motor and premotor cortex. Fiber tracking was terminated when it reached a pixel with an FA value < 0.25 or when the turning angle was > 70°. Note that the procedure described here was used as a default; in several specific cases in which reconstruction was incomplete, a conjunction of only 2 ROIs was performed and/or the FA value was reduced. The decision to do so was based only on clinical and anatomical considerations and was always performed prior to surgery, ruling out any possibility of bias due to feedback of intraoperative findings. Coregistration of the b0 signal intensity volume of the diffusion weighted images with the SPGR volume was conducted using SPM5 software. The generated fibers were saved as a binary mask for superimposing to the SPGR sequence after the coregistration procedure. The new superimposed series were uploaded to the neuronavigation system.

Neuronavigation and Intraoperative Imaging

We used the Sonowand navigation system (SonoWand, Mison) to which the superimposed series composed of the anatomical (fast SPGR) images along with the DT imaging tractography images were uploaded. The skin incision and craniotomy sites were determined after registration of the patient to the neuronavigation system. A baseline US scan was acquired after elevating the bone flap and before opening the dura mater, producing 3D images that were integrated into the navigation database. Several 3D US acquisitions were made intraoperatively to evaluate and compensate for the ongoing process of brain shift. The acquisition of 3D US scans is an extremely easy and rapid procedure. Image acquisition takes about 30 seconds, and image data reconstruction takes an additional 30–60 seconds. Thus, the added imaging time is negligible. As real-time imaging corrects for intraoperative brain shift, it is believed that navigating on an updated set of images is of clear benefit.

Operative Technique

Patients underwent surgery under general anesthesia (20 patients) or standard awake craniotomy (35 patients) with local anesthesia for the craniotomy exposure.

Electrical Cortical Mapping

Direct cortical 50-Hz bipolar stimulation was performed for cortical mapping of cognitive, speech, and motor function (Ojemann cortical stimulator, Radionics, Inc.) by stimulating the cortical surface in 2-mA increment intensities, from a baseline of 4 mA to a maximum of 10 mA or until a functional response was elicited. All bipolar stimulation was accompanied by electrocorticographic recordings with an embedded Silastic 8-contact cortical electrode (AdTech) described below. The brain surface was irrigated with iced Ringer solution if epileptiform activity or seizures were observed concomitant to stimulation. Sedative medications were avoided to allow for uninterrupted functional mapping and clinical evaluation.

Patients who underwent surgery in the awake setting performed all the motor function tests described above before initiating cortical stimulation to establish a functional baseline. Clinical motor dysfunction was determined by a decline from baseline performance noted by the patient and/or an observer. The locations of all stimulation points as well as the points of resection where clinical dysfunction occurred were identified by the neuronavigation system and documented.

Neurophysiological Monitoring

All neurophysiological monitoring was performed with multichannel evoked response units (Axon Eclipse and Epoch XP Neurological Workstations, Axon Systems). A baseline median nerve SSEP trial was preoperatively conducted from 2 cm posterior to the C3 or C4 scalp positions and referenced to the Fz scalp position of the international 10–20 system using subdermal needle electrodes (Axon Systems), following contralateral median nerve stimulation at 25–35 mA with pre-gelled surface electrodes (Axon Systems). Between 50 and 200 traces were averaged for optimizing the signal-to-noise ratio (sweep 50 msecs, scale 1 μsec/division, and bandpass filter 30–750 Hz). The baseline was used as a reference for the subsequent intraoperative phase reversal SSEP method. Intraoperative phase reversal was recorded from the same Silastic 8-contact embedded electrode placed prior to 50-Hz mapping (described above) and over the approximate location of the primary motor cortex, either by direct application or by sliding it subdurally beyond the craniotomy in the direction of the primary motor cortex in a semi-perpendicular orientation. Phase reversal SSEP data were collected simultaneously from the 8 contacts for the purpose of central sulcus identification by using the same recording and stimulation parameters as those used for baseline SSEPs.

For primary motor cortex activation, electrical stimulation was performed with the same electrode array, specifically using the contact corresponding with first inverted N20 waveform on the phase reversal SSEP. In cases in which this could not be executed or in which there was

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### TABLE 3: Preoperative motor function

<table>
<thead>
<tr>
<th>Motor Deficit</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>upper limb monoparesis</td>
<td>17</td>
</tr>
<tr>
<td>lower limb monoparesis</td>
<td>11</td>
</tr>
<tr>
<td>hemiparesis</td>
<td>14</td>
</tr>
<tr>
<td>facial weakness</td>
<td>5</td>
</tr>
<tr>
<td>no motor deficit</td>
<td>28</td>
</tr>
</tbody>
</table>

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no clear reversal, each of the 8 contacts were stimulated individually in a progressive manner (at a rate of 1 stimulation/second between separate contact stimulations), with stepwise increasing intensities of 0.1 mA, to a maximum of 25 mA anodal stimulation (train of 5–7 pulses, 0.5 msec each at 300 Hz). The contact exhibiting the lowest stimulation threshold for producing a dcMEP in at least 1 of 10 channels of contralateral musculature (orbicularis oris, trapezius, deltoid, biceps, wrist extensor, thenar, intercostal, quadriceps, and anterior tibialis muscles) was used as the primary stimulating contact throughout the remainder of the procedure. Recording parameters were set as follows: sweep 10 msec/division, vertical scale 50 μV/second, and bandpass filter 20–3000 Hz. The ipsilateral thenar muscle was used as a control recording. All dcMEP recordings were made using paired subdermal needle electrodes (Axon Systems). Collection of the dcMEP data during resection was set at 1 stimulation every 5–10 seconds to minimize the facilitation effect, epileptogenic risk, and patient discomfort. The stimulation electrode for dcMEPs was set as the anode, with the cathode positioned at an Fz scalp position outside the surgical field. In awake patients, the most distant contact of the set of 8 was chosen as the cathodal return to minimize patient discomfort and interference on the facial MEP channel. During all stimulation sessions, concurrent electrocorticographic activity was recorded from the remaining cortical electrodes to identify cortical afterdischarges or epileptiform activity (1–80 Hz).

Subcortical MEP Stimulation

Throughout the resection process, subcortical stimulation was applied along the border of the tumor resection bed by using a monopolar handheld probe (Inomed; Fig. 1), with the same recording channels and parameters as those used for direct cortical stimulation, except for 2 stimulations/second cathodal stimulation instead of slower anodal stimulation. Stimulation intensity was increased stepwise at 0.1 mA to a maximum of 25 mA or when an scrtMEP was detected. The MEP threshold was determined by the lowest stimulation intensity to result in a reproducible scrtMEP surpassing 50 μV in peak-to-peak amplitude. Once a threshold was confirmed by at least 2 successive reproducible MEP recordings, stimulation was ceased without further increase in the stimulation intensity. Multiple points within the resection cavity were used for subcortical mapping to optimize the estimation of the distance to the CST. Once proximity to the CST was established (any motor response to subcortical stimulation), resection of the tumor was slowly performed, and repeated subcortical stimulations were applied (every few millimeters in depth) until motor responses were elicited at a threshold of 5 mA, which was our target stimulation threshold (corresponding to a distance of 5 mm from the motor tracts).

The precise duration of scrtMEP monitoring was not documented for each case. However, elaborate stimulation (5–10 stimulation points) usually requires about 5–10 minutes. Accordingly, in a typical procedure, the overall time dedicated for stimulation is associated with increased operative time of 15–30 minutes.

Correlation of scrtMEP Threshold With Distance to the CST

Imaging acquisitions were performed with the IOUS system either immediately before or after subcortical stimulations of the resection bed. Side-by-side tractography-based neuronavigation images and analogous IOUS scans were compared according to the corresponding views (Fig. 2). An offset display marker automatically displayed the image at the time of navigation to provide spatial scaling that was used for later measurements. Following acquisition, the navigation probe was positioned at the corresponding stimulation point and angled to best visualize the closest CST (Fig. 3). Screenshots of the side-by-side IOUS/DT imaging were captured and retained for subsequent offline analysis. At least 3 analogous anatomical reference points within the vicinity of the white matter stimulation site were required for each IOUS/DT image set as criteria for inclusion of the image in the distance measurement. Distances to the CST were measured on the images by using the measuring tool in Adobe Photoshop CS4 (Adobe Systems, Inc.; Fig. 2). Calibration for the measuring tool was established with the aforementioned offset markers on each respective image set. Stimulation points that were calculated as < 10 mm from the neighboring cortex were excluded from further analysis to avoid falsely low scrtMEP threshold values due to unwanted cortical activation (“outward activation”) rather than true activation of the deep subcortical CST.

Distances were measured from the plotted stimulation point depicted by the probe’s location on the IOUS-based navigation images, to the closest boundary of the CST as depicted by DT/MR imaging (Fig. 3) after correction by the analogous US scan. Distance values (in millimeters) and threshold values (in milliamperes) were plotted using an XY scatter graph function, and trend lines of several orders (linear, logarithmic, and exponential) were assessed for the lowest respective correlation value ($R^2$) using the Microsoft Excel trend line (Fig. 4).

Clinical Assessment

Motor status was recorded and graded on a scale of 0–5 (0 = no contraction, 1 = flicker or trace contraction, 2 = minimal contraction, 3 = contraction, 4 = brisk muscle contraction, 5 = voluntary movement) using a reproducible scrtMEP, and the lower of the respective correlation value ($R^2$) using the Microsoft Excel trend line (Fig. 4).
2 = movement with gravity eliminated, 3 = movement against gravity, 4 = movement against resistance, 5 = normal strength) at different time points: 1) in the preoperative hospitalization period, 2) in the recovery room immediately postoperatively, 3) at discharge from the hospital (within 3–5 days postoperatively), 4) 2 weeks following surgery, and 5) at the last follow-up (2–11 months after surgery). Motor recovery status was classified as follows: 1) quick, recovery of motor deficit by the time of hospital discharge, within 5 days; 2) intermediate, recovery of motor deficit by the time of the first follow-up at the outpatient clinic within 2 weeks of the procedure; or 3) long-term deficit, no recovery of motor deficit by the time of the latest neurological follow-up.

Correlation Between dcMEP Monitoring Changes and the Postoperative Motor Status

Stability of dcMEP monitoring was classified as follows: 1) stable dcMEP data throughout resection, 2) transient dcMEP attenuation or periods of instability returning to baseline by the initiation of dural closure, 3) persistent significant (> 80%) MEP attenuation, and 4) permanent abolishment of dcMEPs. The dcMEP stability was correlated with the respective postoperative clinical status for each patient.

Statistical Analyses

Statistical analyses were performed using SPSS for Windows, version 12.0 (SPSS, Inc). Correlation coefficients and group differences were analyzed using the Pearson correlation coefficient and independent sample t-tests, with a probability value ≤ 0.05 considered significant.

Results

Correlation of scrtMEP Threshold and Distance to the CST

Thirty-three patients had subcortical stimulation resulting in positive scrtMEP recordings. Sixty-five subcortical stimulation points were assessed: 43 yielded positive MEP recordings and were plotted as threshold stimulation values against the distance to the CST on a XY scatter graph by using Microsoft Excel 97 software. A linear correlation line showed a trend equation of 0.8103 × +1.5897, with the highest coefficient of variability (R² = 0.69), when compared with logarithmic (R² = 0.67) or exponential (R² = 0.53) orders. The average stimulation intensity/distance to the CST ratio was 0.97 ± 0.3 mA/mm. The remaining 22 stimulation points that were > 25 mm from the CST yielded no MEP responses, even at the higher stimulation intensities of 25 mA.

Postoperative Clinical Results

Thirty-seven patients (67%) displayed no postoperative change in their motor status (“stable”), 2 patients (4%) improved, and 16 (29%) displayed an immediate postoperative motor deterioration (Table 4). Six of these 16 patients had a quick recovery (by the time of discharge from the hospital, within 5 days), 3 had an intermediate recovery (within 2 weeks from discharge), and 7 (12.7%) were classified as having a long-term deficit (no improvement at the time of their last follow-up visit). Three patients were not followed up after their predischarge evaluation (none had any apparent motor deficit). The mean duration of follow-up for the entire cohort was 66 days (range 6–323 days). There were no deaths related to the surgical procedures.
Intraoperative assessment of the corticospinal tract

Correlation of Electrophysiological Findings to Postoperative Clinical Status

Direct cortical-stimulated MEPs were attempted in all patients. The subdural electrode could not be placed due to substantial subdural adhesions in 5 patients. Intraoperative detection of variability (instability) in the dcMEP waveforms was considered a possible variable for an impending motor deficit. The occurrence of immediate postoperative motor deterioration was significantly more frequent in patients with cortical MEP instability or abolishment when compared with the stable dcMEP group (p < 0.012 1-sided, binomial test).

The patients were further categorized as true positives (unstable MEP) with postoperative clinical deterioration (8 patients); true negatives (stable or abolished MEP) and no postoperative motor deficits (26 patients); false positives (unstable MEP) and no postoperative motor deficits (10 patients); and false negatives (stable MEP) with significant postoperative motor dysfunction (6 patients). Accordingly, intraoperative MEP instability carried a sensitivity of 62% and a specificity of 72% for predicting an immediate postoperative motor deficit, corresponding to an 84% negative predictive value and a 44% positive predictive value for motor function.

Threshold Subcortical MEP as an Indicator for Postoperative Motor Dysfunction

Subcortical-stimulated MEPs were obtained in 45 patients. Thirty-two remained motor deficit-free (stable or improved motor status), and 27 (84%) of these 32 patients had a minimal subcortical threshold stimulation that produced a motor response > 7 mA. The 16 patients who showed postoperative motor dysfunction were further subcategorized into 2 groups. The first group comprised 6 patients who recovered quickly (prior to discharge from the hospital, within 5 days after surgery). Their minimum scrtMEP threshold was > 6.8 mA. The second group comprised 10 patients who had intermediate or no recovery of motor deficits. Motor evoked potentials were monitored in only 7 of these patients, and 5 of them had a minimum scrtMEP threshold < 3 mA. Of the 7 patients who displayed an scrtMEP value < 3.0 mA, 5 (71.4%) deteriorated immediately after surgery. Two of these 5 patients recovered to their preoperative status within 2 weeks of surgery, and the other 3 remained with a long-term deficit.

Thirty-six (94.7%) of 38 patients who displayed a motor response to stimulation at thresholds > 3 mA did not experience any postoperative motor deficits. Using a 3-mA stimulation threshold value as a predictor of motor function outcome resulted in a sensitivity of 83.3% and a specificity of 94.7%, corresponding to a negative predictive value of 97.3% and a positive predictive value of 71.4% for motor function.

Coincidence of Low Subcortical Stimulation Thresholds and Cortical MEP Instability

Forty patients underwent both dcMEP and scrtMEP recordings. Five (71.4%) of the 7 patients with scrtMEP values < 3 mA displayed periods of unstable or abolished dcMEPs during the course of surgery. Thirty-three patients had scrtMEP values > 3 mA, and the dcMEPs remained stable in 24 of them (72.7%). Setting a scrtMEP cutoff value at < 3.0 mA as a criterion for dcMEP instability yielded specificity and sensitivity values of 92.3% and 35.7%, respectively.
Patients who presented with a motor dysfunction prior to surgery had a higher risk of experiencing new motor deficits postoperatively. Of the 27 patients with a preoperative motor deficit, 11 (40.7%) deteriorated immediately after surgery, and only 4 of them returned to baseline within 1 month. Conversely, only 5 (17.9%) of 28 patients with no preoperative deficit demonstrated new motor deficits after surgery, and 4 of them underwent a full motor recovery within 2 weeks of surgery (4% of long-term postoperative deficits).

**Awake Versus General Anesthesia**

Whether or not the procedure was done with the patient under general anesthesia had no significant impact on the immediate postoperative motor status, extent of resection, or threshold intensity for eliciting a motor response with subcortical stimulation. Four patients undergoing awake operations who had exhibited unstable MEPs with new motor deficits after surgery were shown to have such deficits during surgery. In the patients who underwent general anesthesia, a total intravenous regimen was administered, including propofol and remifentanil for induction and maintenance, while avoiding the use of halogenated inhalational agents at all times.

**Discussion**

There is an ongoing search for methods to achieve maximal resection of intraaxial lesions, especially glial tumors, while minimizing the risk of new neurological deficits. Functional imaging, tractography, neuronavigation, and electrophysiological stimulation techniques have become routine practice in many places for this reason. Enhanced methods to preserve the CSTs were achieved using tractography-based neuronavigation along with subcortical stimulation. Attempts to evaluate the actual distance between the tumor and the CST have been hampered by inherent brain shift. The current study represents the first attempt to evaluate that distance by using the threshold of subcortical monopolar stimulation with real-time intraoperative imaging for the correction of brain shift. We evaluated the distance from the CST as a variable of the threshold of subcortical stimulation needed to elicit a motor response under the premise that the spread of outward stimulation is relative to the delivered intensity, and as such, shorter distances to subcortical motor fibers will require less current to overcome the resistance properties of subcortical tissue. Mikuni et al. compared subcortical MEP recordings and fiber tracking and found that with 50-Hz bipolar stimulation at a constant intensity, a distance < 7 mm correlated with positive motor responses, while distances beyond 13 mm did not produce a motor response. They concluded that stimulation at a distance of 1 cm from the CST would produce a motor response in most patients. Kamada et al. recently found a nonlinear correlation between the distances to the CST and the monopolar threshold levels. These authors evaluated the distance from the stimulation point to the CST by applying the same methods we used with DT/MR imaging—based navigation, but they evaluated the distance to the CST based on postoperative DT/MR imaging, a methodology with inherent limitations of precision from both radiographic and spatial perspectives.

In an attempt to overcome the limitation of brain shift, we acquired several sets of real-time 3D US images during a surgical procedure to add that information to the preoperative tractography-based neuronavigation data.
cally, we tried to compare the new images to the preoperative imaging in a quality-controlled fashion by identifying at least 3 surrounding analogous anatomical landmarks on each matching DT/MR imaging and IOUS image set for precise orientation. Images of low quality or those with fewer than 3 clear landmarks within a reasonable range of the target were excluded. We plotted MEP thresholds against distance in millimeters and demonstrated a linear correlation with an \( R^2 \) value of 0.69. This result provides the surgeon with a more accurate estimation of the distance to the CST that roughly corresponds to a distance of 1 mm for each 1-mA threshold increment.

There are limitations to the current study. First, the tumor and the edema that are usually located in proximity to the CST might influence the reliability of the tract's computation images when using DT imaging tractography on preoperative imaging.\(^5\),\(^21\) To minimize this concern, the FA threshold values were adopted individually per patient to yield the best reconstruction. Specifically, when the tract was only partially reconstructed using the default FA value (0.25 arbitrary units [AU]), the FA was reduced up to 0.15 AU to achieve a more continuous delineation of the tracts. In addition, because we used a conventional single-tensor approach for tractography, the reconstructed fiber tract probably represented only part of the projections from the motor cortex. This limitation is attributable to the well-documented presence of crossing fibers. At corona radiata levels, while there is a good representation of the medial motor fibers (that is, the legs), we observed partial representation of the lateral fibers (that is, the face and arms). At deeper levels like the internal capsule, DT imaging tractography appropriately suited the size and morphology of the anatomical properties of the capsule. Taking this into account, our postoperative analysis exclusion criteria discounted superficial stimulation points that would have been affected by this limitation, leaving deeper and more accurately represented sections of the CSTs included for analysis. Several alternative approaches for tractography are currently being examined in an attempt to obtain a full reconstruction of the CSTs.\(^23\)

Patients who exhibited deterioration after surgery, despite having a high scrtMEP threshold, most likely suffered from a vascular injury. Two such patients who harbored temporomandibular tumors were identified in our population. Kombos et al.\(^15\) investigated the clinical impact of real-time intraoperative neurophysiological assessment in the resection of tumors in the vicinity of the CST and showed that changes in the latency and amplitude of cortical MEP recordings served as warning criteria in addition to having prognostic value. Keles et al.\(^16\) claimed that subcortical mapping of the CSTs allowed safer resection: 7.3% of their reported patients whose subcortical pathways were detected experienced permanent motor deficits, as compared with only 2.1% of the patients whose subcortical pathways were not detected. Moreover, Bello et al.\(^1\) concluded that the combined methods of DT imaging and subcortical stimulation might enhance surgical safety and maintain a high rate of functional preservation. These authors advocated a procedure of routinely alternating tumor resection with subcortical stimulation. In these aforementioned reports, the subcortical mapping method was used in a "binary" fashion, in which tumor resection was terminated whenever there was a motor response to stimulation at a set intensity,\(^9,\(^44\) rather than the quantitative approach of graded stimulation with MEP threshold establishment.

We also tried to evaluate motor outcome according to neurophysiological assessment and monitoring in an attempt to identify specific red flags to alert the surgeon operating in the vicinity of the CSTs. We found neurophysiological patterns that met these criteria. For example, MEP instability or abolishment was associated with postoperative motor deterioration (sensitivity of 62% and specificity of 72%). Our data also indicated that patients had a favorable motor outcome when the threshold stimulation was > 3 mA (sensitivity of 83% and specificity of 95%). This latter finding was supported by the relationship between dcMEP stability and a threshold of < 3.0 mA for eliciting a motor response, with a low subcortical MEP threshold value verifying interrupted dcMEP as a true indication of surgical proximity and impending damage to the CST. Intraoperative MEP instability has limited predictive value for immediate postoperative motor deficits, with a sensitivity of 62% and a specificity of 72%. However, cortical MEPs do provide a means of continuous intraoperative monitoring that may alert the surgeon to imminent damage to the motor pathway. Using scrtMEPs, we have found that a low stimulation threshold (< 3 mA) significantly correlated with a postoperative motor deficit. The cutoff point of 3 mA was associated with a sensitivity of 83.3% and specificity of 94.7%, values that are clearly superior to those derived from cortical MEP data. As the threshold level for scrtMEPs increased, the sensitivity and specificity for predicting outcome decreased.

Multiple points within the resection cavity were used for subcortical mapping to optimize the estimation of the distance to the CST. Once proximity to the CST was established (any motor response to subcortical stimulation), resection of the tumor was performed slowly while repeated subcortical stimulations were applied (every few millimeters in depth) until motor responses were elicited at a threshold of 5 mA, which was our target stimulation threshold (corresponding to a distance of 5 mm from the motor tracts). This mode of tumor resection has been established since assessing the data presented here and serves as our standard procedure for the resection of tumors adjacent to the motor pathways.

It is interesting to note that our methodology was effective regardless of whether patients underwent surgery while awake or under general anesthesia. We were unable to find significant differences in postoperative motor status, extent of resection, or threshold intensity for eliciting a motor response with subcortical stimulation. In theory, however, the electrophysiological excitability of the CST in awake patients should be higher than in anesthetized patients, because of the absence of anesthetic-mediated inhibition, and would warrant investigation into differences in electrophysiological interpretation of cortical and subcortical motor responses in each context. The lack of detectable differences in clinical outcomes between these 2 groups suggests that resection with neurophysiological guidance in anesthetized patients is as comparatively safe as in awake patients.
Conclusions

Combining elaborate neurophysiological assessment, tractography-based neuronavigation, and updated 3D US images provides more accurate localization of the CST and enables aggressive, but safer, resections of tumors in proximity to the CST than other methods currently in use. The linear correlation between the distance of the stimulated point to the CST and the threshold of subcortical stimulation provides an intraoperative tool that surgeons can use to enhance the safety of the surgical procedure and preserve motor function.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conceptualization and design: Ram, Nossek, Korn, Constantini. Acquisition of data: Ram, Nossek, Korn, Shahar, Kannan, Yaffe, Marcovici, Ben-Harosh, Ben-Ami, Weinstein, Shapiro-Lichter, Hendler. Analysis and interpretation of data: Ram, Nossek, Korn, Shahar, Yaffe, Marcovici, Ben-Ami, Weinstein, Shapiro-Lichter, Hendler. Drafting the article: Nossek, Korn, Shahar, Yaffe, Marcovici, Ben-Ami, Weinstein, Shapiro-Lichter, Hendler. Critically revising the article: Ram, Nossek, Korn, Shahar, Constantini. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Nossek, Korn. Study supervision: Ram.

Acknowledgment

The authors thank Ms. Esther Eshkol for her editorial assistance and Ms. Odeya Marmor for her assistance in collecting the intraoperative neurophysiology data.

References


Manuscript submitted April 26, 2010. Accepted August 2, 2010.

Please include this information when citing this paper: published online August 27, 2010; DOI: 10.3171/2010.8.JNS10639. Address correspondence to: Zvi Ram, M.D., Department of Neurosurgery, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel. email: Zviram@tasmc.health.gov.il.