Facilitating complete resection of intrinsic motor cortex glioma with titration of high-frequency cortico-subcortical mapping train count informed by navigated transcranial magnetic stimulation: illustrative case

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BACKGROUND The dilemma of neuro-oncological surgery involving suspected eloquent cortex is to maximize the extent of resection while minimizing neurological morbidity, referred to as the “onco-functional balance.” Diffuse lower-grade gliomas are capable of infiltrating or displacing neural function within cortical regions and subcortical white matter tracts, which can render classical anatomic associations of eloquent function misleading.

OBSERVATIONS This study employed presurgical navigated transcranial magnetic stimulation (nTMS) to determine the motor eloquence of a diffuse lower-grade glioma at the superior frontal gyrus extending and intrinsic to the primary motor cortex in a 45-year-old female. Positive nTMS findings were confirmed intraoperatively with high-frequency direct cortico-subcortical stimulation (HF-DCS). Modification of the HF-DCS train count from train-of-five to train-of-two permitted resection beyond classic anatomical boundaries and conventional HF-DCS safe stopping criteria.

LESSONS Anatomical correlates of function can inaccurately inform the surgical management of diffuse lower-grade glioma, which represents the utmost opportunity for progression-free survival. Integrating an individually tailored nTMS-DCS surgical strategy contributed to complete resection, negating the requirement for adjuvant therapy. Serial nTMS follow-up may assist with the characterization of tumor-induced functional reorganization.

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KEYWORDS direct cortical stimulation; eloquent tumor surgery; supratentorial glioma; maximal resection; onco-functional balance

The challenge of brain tumor surgery involving the eloquent cortex is maximizing the extent of resection while minimizing neurological morbidity, referred to as the “onco-functional balance.” Clinical approaches and philosophies are widely heterogeneous with regard to intra-axial supratentorial tumor surgery; however, it is universally accepted that safe and maximal resection with the avoidance of significant ischemic or neurological sequelae is the primary goal.

Gliomas can be located within close proximity or attached to functionally important cortical areas and can also infiltrate subcortical white matter tracts. Manipulation or resection near to or within functional areas during surgery can result in transient or permanent neurologic injury, which can be severely debilitating and contribute to a poorer prognosis. The surgical management of adult diffuse low-grade glioma (LGG), in particular, represents an incomparable opportunity for progression-free survival, though surgery is not curative.

Adult diffuse LGGs (typically World Health Organization [WHO] grade 2) grow slowly over time and are capable of inducing cortical plasticity, with some recommending that tumor resection be staged to preserve eloquence after observing functional reorganization between procedures.1 Although LGG patients have more favorable survival rates than patients with high-grade glioma (HGG; WHO grade 3–4), LGG is a uniformly fatal disease with survival averaging approximately 7 to 10 years2 and reports of up to 15 years,3 with all LGGs systematically evolving toward higher-grade anaplastic transformation.4

The infiltrative character of LGG renders complete resection without neurologic deficit challenging. Criteria for the surgical management of suspected eloquent tumors often involve direct cortico-subcortical

Abbreviations: CST = corticospinal tract; DCS = direct cortico-subcortical stimulation; FLAIR = fluid-attenuated inversion recovery; fMRI = functional MRI; HF-DCS = high-frequency DCS; LF-DCS = low-frequency DCS; LGG = low-grade glioma; M1 = primary motor cortex; MEP = motor evoked potential; SMA = supplementary motor area; sMEP = subdural motor evoked potentials; monoTcMEP = monophasic transcranial motor evoked potential; MRI = magnetic resonance imaging; nTMS = navigated transcranial magnetic stimulation; WHO = World Health Organization.

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stimulation (DCS) mapping for identification and avoidance of eloquent cortical and subcortical regions. Traditionally, the indication for DCS mapping considers anatomical correlates of function or landmarks classically associated with function, often involving periorbital or perisylvian cortex.

Literature suggests that the contemporary management of adult diffuse LGG patients may consider a transient neurological injury in lieu of an increased resection opportunity, which increases the prospect of progression-free survival. While the corticospinal system is widely considered to demonstrate less neuroplastic potential in comparison to language function that is suspected to be organized in a hodotopic or connectomic fashion, interindividual variability has still been described in glioma patients at the cortical level. This can render the functional delineation of the primary motor cortex (M1) challenging, which can contribute to an insufficient resection or, contrarily, neurological injury.

Intraoperative cortico-subcortical mapping and monitoring is intended to functionally identify motor and language regions during neuro-oncological surgery and has long since been associated with increased resection rates and decreased neurological morbidity. With regard to the corticospinal system, bipolar low-frequency DCS (LF-DCS) mapping is usually measured via visual confirmation of a muscle twitch, whereas monopolar high-frequency DCS (HF-DCS) mapping is capable of generating sub-clinical motor evoked potentials (MEPs) via electrodes within relevant muscle groups, which promotes the objective detection and measurement of cortical and subcortical regions associated with voluntary movement. Although LF-DCS has been an effective technique for motor mapping widely described since the Ojemann era, adoption of HF-DCS has provided a degree of objectivity during analysis in addition to the option for asleep craniotomy under general anesthesia. This ultimately has contributed to preserving LF-DCS for cognitive mapping due to its inhibitory capabilities during behavioral tasks necessitated by awake craniotomy.

Navigated transcranial magnetic stimulation (nTMS) is an emerging functional neuroimaging modality that incorporates noninvasive magnetic stimulation via a handheld biphasic coil partnered with a stereotactic targeting system co-registered with the patient's magnetic resonance imaging (MRI) scan, in order to target peritumoral cortex and relevant cortical anatomy associated with motor and language function. nTMS shares an electrophysiological profile that has been shown to yield a close corroboration with DCS at the cortical and network level, in addition to greater sensitivity for motor function when compared with functional MRI (fMRI).

Recently, Rossi et al. described a novel method of HF-DCS designed to safely maximize resection of tumors intrinsic to the precentral gyrus or M1, highlighting that posterior and anterior borders share differing corticospinal excitability. They posited that the anterior M1 component with lower corticospinal excitability could be resected without compromise of voluntary motor function postoperatively, provided that HF-DCS parameters were modified to reduce the focality of stimulation for detection of the posterior M1 component. The authors highlighted that this functional delineation is supported by animal studies in addition to DCS studies in awake patients which highlighted that posterior precentral gyrus stimulation yielded muscle activation whereas anterior precentral gyrus stimulation resulted in suppression of motor function.

Importantly, Rossi et al. highlighted that this rostrocaudal demarcation was preserved for lesions outside of M1 and not infiltrating the corticospinal tract (CST), yet half of patients with lesions intrinsic to M1 encountered distorted somatotopic distribution irrespective of histopathology or volume, and the remaining half did not. Irrespective of somatotopic discordance, motor function was preserved and the disparity was suggested to be indicative of functional reorganization. To facilitate this measurement, the authors described the titration of HF-DCS train count at the cortical and subcortical level from a train-of-five (TO5) to train-of-two (TO2) to distinguish safe stopping criteria within gray and white matter tissue with a maximum safe stopping criterion of approximately 3 mA following modification.

Illustrative Case

History and Examination

A 45-year-old female presented with intermittent headache and was referred for MRI, which demonstrated a nonenhancing 20 × 16 mm T2-hyperintense lesion at the junction of the left superior frontal gyrus posteriorly and left precentral gyrus medially. Radiological findings suggested that the CST superiorly traversed at the inferomedial margin of the lesion and was suspected to be involved at the medial aspect (Fig. 1).

The consultant neurosurgeon (A.P.) referred the patient for nTMS (Nexstim OYJ) to distinguish eloquent motor regions involving or adjacent to the lesion, as well as the possibility of interhemispheric imbalance of the corticospinal system as indicated via the interhemispheric resting motor threshold ratio, and finally, to establish functional seed points for DTI-fiber tracking for intraoperative reference.

Presurgical Mapping

During the nTMS session, surface electrodes (Spes Medica) were applied to the brachioradialis ("arm"), abductor pollicis brevis ("hand"), tibialis anterior ("leg"), and abductor hallucis ("foot"). Stimulation included regions involving the superior frontal gyrus, middle frontal gyrus, precentral gyrus, postcentral gyrus, and superior parietal lobe as defined by Corina's cortical parcellation system. Initial targeting of the precentral gyrus "hand knob" at the right hemisphere yielded positive arm (57–1332 µV) and hand (56–1318 µV) MEP responses between stimulation thresholds of 29% and 35% maximum stimulator output (MSO; 22–64 V/m electric field) and no evidence of white matter activation with an upper-extremity resting motor threshold of 29% MSO.

Post hoc analysis of all stimulation sites indicated a clear demarcation of the motor hotspot predominantly focused within the pre- and postcentral gyri (Fig. 2A). Stimulation then proceeded toward the medial motor cortex with the coil oriented perpendicular to the longitudinal fissure. Lower-extremity MEPs were observable at an increased stimulation intensity of 65% MSO (66-90 V/m electric field) at the leg (60–2023 µV) and foot (51–378 µV; Fig. 2B). Subsequent testing of lesional cortex aided with a 5 × 5–mm grid at the resting motor threshold of 29% MSO indicated eloquent motor regions at the lateral and posterior aspects of the tumor margins.

The precentral gyrus "hand knob" at the right contralesional hemisphere was subsequently targeted, with no pathologic disparity observed in comparison to the right hemisphere with regard to cortical excitability, somatotopic organization, and amplitude and magnitude of responses. The resting motor threshold at the right hemisphere was comparable to the left (30% versus 29% MSO) with MEPs ranging between 53 and 1409 µV (48–62 V/m). This falls within "normal" interhemispheric resting motor threshold ranges.

Positive MEP data at the ipsilesional and contralesional hemisphere were exported for nTMS-fiber tractography and surgical planning.
planning (Medtronic StealthStation S8, Medtronic, Inc.). The patient was counseled preoperatively with nTMS findings and informed of the possibility of neurological injury irrespective of modified DCS parameters and elected for a safe and maximal resection.

**Intraoperative Mapping**

Cortico-subcortical mapping and monitoring parameters and workflow have been described elsewhere by the primary author. In the current study, this included sensorimotor phase reversal (SPR) for delineation of pericentral anatomy, anodic monopolar HF-DCS for localization of eloquent motor cortical topography, direct cortical subdural motor evoked potentials (sMEPs) for continuous CST monitoring, cathodic monopolar HF-DCS for localization of descending corticospinal white matter tract pathways, and monophasic transcranial MEPs (monoToMEPs; Medtronic NIM-Eclipse, Medtronic, Inc.). Channels not used for sMEP monitoring were used for electrocorticography (ECoG). Cathodic HF-DCS for subcortical mapping was delivered interchangeably via a monopolar suction cannula probe (inomed medizintechnik GmbH) and clip attachment to the ultrasonic aspirator (Soring GmbH).

The anesthesia protocol included total intravenous anesthesia combining propofol and remifentanil. Induction was achieved with a continuous infusion of remifentanil at 0.10–0.20 mg/kg/min and maintained with 0.25–0.40 mg/kg/min. Dexamethasone was administered, and the mean arterial pressure was kept above 85 mm Hg throughout the operation. No muscle relaxants were used after induction and intubation, and a bite block was positioned. The patient was positioned
supine with slight head tilt secured in a Mayfield head clamp. The patient was started on Keppra (levetiracetam) 500 mg 3 days prior to surgery.

SPR was configured in a referential montage and indicated a positive dipole between channels 2 and 3 of the subdural electrode. HF-DCS at the cortical level indicated a resting motor threshold of 12 mA. Functional localization of eloquent motor areas was concordant with presurgical nTMS findings for the upper and lower extremities. Subsequent sMEP testing in the same configuration yielded large-amplitude (~1 mV) polyphasic MEP responses at 15 mA at the arm and hand, which were reproducible. monoToMEPs were also incorporated at 220 V (TO5, 75 µs pulse duration, 333 Hz), with no evidence of interhemispheric activation of the ipsilesional hemisphere. Several sequences of anodic HF-DCS were conducted to ensure a safe entry zone with negative MEPs.

Following the initial stage of the corticectomy, cathodic HF-DCS testing at 5 mA contributed to a low-amplitude response on the upper extremities (~200 µV). Intensity was subsequently titrated to 3 mA, with significantly lower-amplitude responses observed (~50 µV). Debulking continued with subcortical mapping, often with each quadrant of the lesion being titrated between 3 and 5 mA TO5 prior to moving in a slightly different aspect of resection within the cavity. Intermittent subcortical mapping at 10 mA confirmed activation of the entire contralateral hemibody due to direct excitation of the CST. When positive MEP responses were observed at 3 mA TO5 in each quadrant, the train count was reduced to TO2 with no positive MEP responses observed (Fig. 3). Microsurgical debulking continued with subcortical mapping until lower-extremity responses (~50 µV at the leg and foot) were consistently observed at 3 mA TO2, prompting hemostasis and closure. No intraoperative seizures were observed either clinically or associated with cortico-subcortical stimulation.

Postoperative imaging revealed complete resection with no T2/fluid-attenuated inversion recovery (FLAIR) hyperintense residual tumor, and the patient experienced a suspected supplementary motor area (SMA) syndrome from which she had largely recovered within 1 week. Histology revealed a WHO grade 2 oligodendroglioma, IDH mutation, 1p19q co-deleted, TERT promoter mutation. Given the extent of resection, the patient was not referred for adjuvant radiation therapy and chemotherapy. The patient remained on serial imaging, including nTMS motor mapping for surveillance of tumor-induced neuroplastic changes (Fig. 4), with no tumor recurrence observed at 12 month follow-up.

**Patient Informed Consent**

The necessary patient informed consent was obtained in this study.

**Discussion Observations**

Gliomas are often located in proximity or attached to functionally important cortical areas and subcortical white matter tracts. Early surgical intervention and gross-total resection (GTR) are well substantiated in prolonging overall survival in LGG. This study employed presurgical navigated nTMS to determine the motor eloquence of a diffuse LGG at the superior frontal gyrus extending and intrinsic to the primary motor cortex in a 45-year-old female. Positive nTMS findings were exported to generate individually tailored nTMS diffusion tensor imaging fiber tractography for preoperative risk stratification and intraoperative guidance. nTMS-tractography data informed

![FIG. 3. A: Registration of cathodic HF-DCS CST activation (automated tracts in orange) via intraoperative navigation with titration of train count. B: Cathodic HF-DCS TO5 with lower-extremity activation. C: Cathodic HF-DCS TO2 with lower-extremity activation after period negative mapping following titration of train count.](image-url)
the operative strategy and likelihood of eloquent motor involvement at the posterior tumor margin infiltrating the precentral gyrus and descending CST, contributing to the intraoperative modification of the HF-DCS train count from TO5 to TO2 which permitted resection beyond classical anatomic boundaries and conventional HF-DCS safe stopping criteria.

Criteria for safe and maximal resection of eloquent supratentorial lesions incorporate a multitude of factors that take into consideration opportunities to promote a favorable onco-functional balance, including age, neurological status, seizure frequency, body habitus, and psychological status. In the current study, a number of these variables were met, including early detection, smaller tumor volume, nonadvanced age, and no seizure activity.

Research suggests that when DCS mapping is individually tailored for each patient, there is a unique opportunity to promote progression-free survival.\(^{27}\) When we combined nTMS with modified HF-DCS parameters, our experience supports this postulation. While this titration was not necessary at the immediate cortical level as described by Rossi et al., it enabled an additional approximate 1 cm\(^3\) of tumor resection. Specifically, once the resection had reached the safe stopping criteria of 3 mA TO5, switching to T02 facilitated a further ~1 cm\(^3\) to be resected until reaching the safe stopping criteria of positive MEP responses greater than 50 µV at 3-mA amplitude.

In addition to these factors, electing to refer the patient for nTMS informed both the patient and the surgical team to consider the stratification of risk associated with neurological morbidity, which has also been reported to increase gross total resection rates and progression-free survival in LGG patients.\(^{28}\) In contrast, fMRI may have indicated a similar but less precise cortical region of eloquent activation; however, positive nTMS data have repeatedly demonstrated a closer alignment in comparison to gold-standard DCS findings.\(^{29-31}\) nTMS-tractography also affords a more accurate calculation of risk according to functionally defined proximity to adjacent white matter tracts.\(^{32}\) Similarly, resection within nTMS-positive motor regions has been shown to contribute to a greater risk of permanent neurological injury.\(^{33}\) While we have described a modified HF-DCS train count to discriminate between anterior and posterior M1 for resection without injury, it remains unclear if nTMS is capable of achieving discrimination between anterior and posterior motor excitability.

Although there have been recommendations to define a safe stopping criteria at 4–5 mA,\(^{23,34}\) the very same research also stipulates that safe resection is possible with lower thresholds only when the procedure incorporates expert electrophysiological personnel partnered with a consultant neurosurgeon capable of rapid interpretation and immediate adaptation, each of which demands a steep learning curve. The ubiquitous inclusion of some form of brain mapping cannot be considered a surrogate for avoidance of iatrogenic injury, and approaches relating to safe and maximal resection in adult LGG patients must also consider the risk of neurological injury with insufficient recovery. The mechanism of activation associated with a reduced monophasic train count, for example, must also consider increased risk of mechanical or ischemic insult of the CST.

Brain cancer patients, especially those with LGG, may have already undergone functional reorganization prior to surgical treatment; thus, invasive functional mapping data may not reflect the native, canonical organization of the nondiseased brain. This is supported by an increasing volume of emerging neuroimaging data that highlight the unpredictability relating to the localization of motor, language, and cognitive function in glioma patients\(^{35-37}\) in addition to numerous studies employing nTMS.\(^{38,6}\) Increasing data also support the therapeutic capabilities of nTMS for rehabilitation following iatrogenic ischemic injury to the CST contributing to enhanced transcallosal inhibition,\(^{39}\) though there are insufficient findings to suggest that similar therapeutic benefit is observed in patients.

**FIG. 4.** nTMS data for upper extremities and lower extremities 6 months post surgery with varying peak-to-peak amplitudes, per ongoing surveillance of neuroplastic reorganization. rMT = resting motor threshold.
with SMA syndrome. Intact sMEP data at hemostasis and positive nTMS data following surgery, however, are highly encouraging prognostic biomarkers associated with recovery of SMA syndrome.

Interestingly, positive nTMS data in this study were not exclusively confined to the precentral gyrus in the ipsilesional or contralesional hemispheres as classically anticipated. The notion of “somatotopic discordance” relates to the misalignment of eloquent motor function at the cortical level of either hemisphere suspected to be associated with oncological disease in addition to the possibility of homologous inter-hemispheric compensation of the corticospinal system, also recently described as a “ship and anchor” theory. Indeed, the “anchor” of the largest nTMS-positive motor responses in this study were not designated to the anterior aspect of the precentral gyrus, which informed our indication to use a modified train count to safely resect within the anterior precentral gyrus.

Recent studies have also highlighted the neuroplastic potential of various brain regions that undergo reorganization between repeat surgical procedures, which challenges the classical but reductionist anatomic localization of motor and language function in patients harboring supratentorial glioma. This patient remains on serial nTMS follow-up in conjunction with routine MRI surveillance in an attempt to characterize motor functional reorganization.

During the era of the Ojemann stimulation technique, mapping of movement and language mapping in supratentorial glioma surgery did not necessarily incorporate electrophysiological biomarkers associated with function. It is imperative to highlight that, in contrast, “not all mapping is created equal”; the advent and adoption of high-frequency DCS protocols, comprehensive monitoring modalities, and intraoperative seizure detection and management strategies have permitted the objective measurement of eloquent motor—and on occasion, language—regions without the requirement for awake surgery. The integration of functional brain mapping tools such as nTMS with contemporary cortico-subcortical mapping and monitoring in this instance provided a comprehensive portrait of oncologically impacted function that guided surgical management.

This study is rather obviously limited by a single-patient cohort. We also recognize that while there are inherent risk stratification advantages with nTMS for the surgical management of suspected eloquent glioma, not all neurosurgical centers have access to this emerging functional neuroimaging modality. Intraoperative optimization of mapping parameters alone may facilitate greater resection opportunities such as that we have described, provided that appropriate clinical indication prerequisites are met. Nonetheless, we agree with an increasing volume of literature supporting an individually tailored and multimodal integration of nTMS, nTMS tractography, advanced cortico-subcortical mapping and monitoring with the emerging prospect of postoperative therapeutic neuromodulation to promote positive patient outcomes in neuro-oncological surgery.

Lessons

Anatomical correlates of function can inaccurately inform the surgical management of diffuse LGG, which represents the utmost opportunity for progression-free survival. Integrating an individually tailored nTMS-DCS surgical strategy contributed to complete FLAIR resection, negating the requirement for adjuvant therapy. Serial nTMS follow-up may assist with the characterization of tumor-induced functional reorganization.

References


**Disclosures**

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**

Conception and design: Hamer. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Criticaly revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Hamer.

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