

## Transcranial magnetic stimulation tractography and the facilitation of gross total resection in a patient with a motor eloquent glioblastoma: illustrative case

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**BACKGROUND** In patients with perieloquent tumors, neurosurgeons must use a variety of techniques to maximize survival while minimizing postoperative neurological morbidity. Recent publications have shown that conventional anatomical features may not always predict postoperative deficits. Additionally, scientific conceptualizations of complex brain function have shifted toward more dynamic, neuroplastic theories instead of traditional static, localizationist models. Functional imaging techniques have emerged as potential tools to incorporate these advances into modern neurosurgical care. In this case report, we describe our observations using preoperative transcranial magnetic stimulation data combined with tractography to guide a nontraditional surgical approach in a patient with a motor eloquent glioblastoma.

**OBSERVATIONS** The authors detail the use of preoperative functional and structural imaging to perform a gross total resection despite tumor infiltration of conventionally eloquent anatomical structures. The authors resected the precentral gyrus, specifically the paracentral lobule, localized using intraoperative mapping techniques. The patient demonstrated mild transient postoperative weakness and made a full neurological recovery by discharge 1 week later.

**LESSONS** Preoperative functional and structural imaging has potential to not only optimize patient selection and surgical planning, but also facilitate important intraoperative decisions. Innovative preoperative imaging techniques should be optimized and used to identify safely resectable structures.

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**KEYWORDS** glioma; motor eloquent; TMS tractography; intraoperative mapping

Surgical planning is critical for patients with motor eloquent tumors. Surgeons must balance maximizing the extent of resection with minimizing postoperative neurological morbidity, the onco-functional balance. Surgeons have traditionally used structural anatomical imaging for surgical indications, patient selection, and preoperative planning. Diffusion tensor imaging (DTI) tractography is a widely used processing technique to visualize white matter tract (WMT) pathways for surgical planning.<sup>1</sup> However, recent data have shown that anatomy may not predict surgical eloquence, indicating the importance of functional data.<sup>2</sup> Transcranial magnetic stimulation (TMS) is a preoperative, non-invasive mapping modality that can use magnetic stimulation to localize

the functional motor cortex. Recent publications have described the feasibility of using TMS data for the cortical region of interest (ROI) instead of anatomical markers such as the precentral gyrus, which has traditionally been the gold standard.<sup>3</sup>

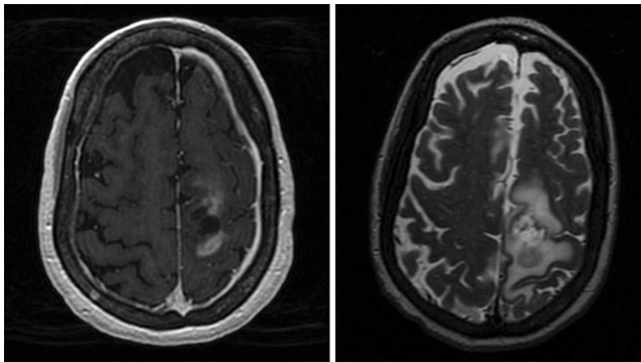
Recent work at our institution has further elucidated the difference between these DTI tractography processing approaches, showing TMS points and WMTs significantly displaced from the precentral gyrus, supporting previous studies documenting glioma-induced neuroplasticity.<sup>4</sup> We found extremely high negative predictive value (97%) of TMS tractography for predicting permanent deficits. In other words, preserving TMS identified corticospinal fibers preserves

**ABBREVIATIONS** DTI = diffusion tensor imaging; FA = fractional anisotropy; GTR = gross total resection; MRI = magnetic resonance imaging; ROI = region of interest; SSEP = somatosensory evoked potential; TMS = transcranial magnetic stimulation; WMT = white matter tract.

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**FIG. 1.** Preoperative axial T1-weighted contrast-enhanced (left) and T2-weighted contrast-enhanced (right) MRI.

neurological function, regardless of location. Additionally, we showed that TMS points without connecting WMT identified at a specific fractional anisotropy (FA) threshold can be safely resected.<sup>5</sup> These studies and recent experiences at our institution have called into question traditional management of these tumors. Here we document our alternative approach to a patient with a high-grade glioma in the eloquent peri-rolandic motor cortex.

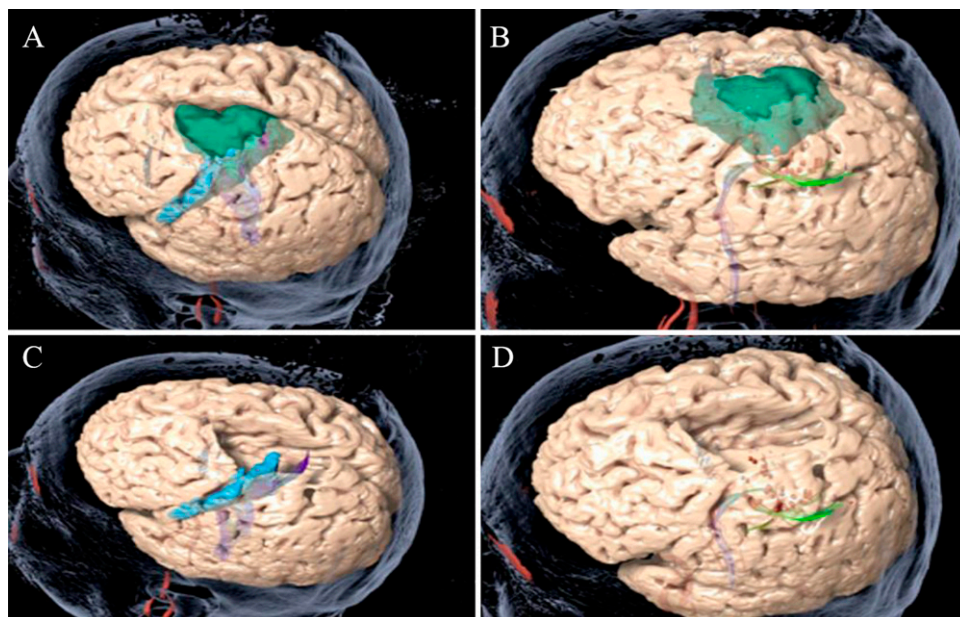
### Illustrative Case

A right-handed female in her 60s with a history of breast cancer and alcohol-related seizure disorder was seen in the neurosurgery clinic as a referral following a magnetic resonance imaging (MRI) scan showing the presence of an expansile mass consistent with

an infiltrating glioma in the left superior frontal region. The patient's neurological examination was significant for a moderate right lower extremity monoparesis. Given the imaging findings she was scheduled for resection of the mass.

The tumor was in the left superior frontal lobe and extended anteriorly from the precentral gyrus into the supplementary motor area, as shown in Figs. 1 and 2. The surgical plan initially was to perform the operation under general anesthesia and proceed with a subtotal resection to avoid the eloquent motor cortex defined by the anatomical precentral gyrus. However, WMTs identified using TMS points as the cortical ROI only connected to TMS points distant from the tumor, as shown in Fig. 2, suggesting that a safe gross total resection (GTR) may be feasible. Accordingly, we changed the approach, deciding to perform an awake craniotomy and pursue a more aggressive resection.

During the case, a  $2 \times 4$  grid to monitor somatosensory evoked potentials (SSEPs) was used to identify the central sulcus and precentral gyrus. No direct cortical stimulation was performed due to seizure risk from medical comorbidities. We proceeded with careful resection while the patient was performing motor tasks with her right hand and foot. From a cortical perspective, we removed the identified precentral gyrus, specifically the anterior portion of the paracentral lobule, as well as structures extending down the precentral gyrus toward the hand knob with no subsequent neurological deficits. Subcortically, direct stimulation was used to identify functional boundaries in the surgical cavity. Positive motor evoked potential responses in both the upper and lower extremity were found in the resection cavity with a stimulation threshold as low as 1.8 mA. The postoperative examination showed slightly weakened right lower extremity weakness for 3 days, but her neurological



**FIG. 2.** Three-dimensional (3D) reconstructions of preoperative imaging show the precentral gyrus (A, blue) and anatomical tractography penetrating the tumor (green), as well as TMS points (B, red) spanning the tumor; however, the WMTs only connect to the inferior portion of the TMS cortex, distant from the tumor. 3D reconstructions of postoperative MRI overlaid with the preoperative MRI show the resection cavity in the context of the preoperative precentral gyrus and anatomical tractography (C) and in the context of TMS points and TMS tractography (D).

exam returned to baseline by the time she was discharged a week later. At last follow-up, 1 month postoperatively, she showed sustained functional capacity with improved right lower extremity weakness compared to her preoperative examination.

## Discussion

Reports in the neuroscience literature have established that the paracentral lobule, as the most medial region of the precentral gyrus, controls motor innervations of the contralateral lower extremity.<sup>6</sup> These studies have led to assumed surgical eloquence and preservation of this region when resecting peri-rolandic tumors. Additionally, previous work has shown that SSEPs can reliably localize the central sulcus intraoperatively, allowing the surgeon to visualize the precentral gyrus directly.<sup>7</sup>

## Observations

Upon preoperative imaging, the tumor infiltrated many structures presumed eloquent: the paracentral lobule, anatomically defined corticospinal fibers, and TMS points. Intraoperative mapping results also seemed to preclude a GTR. The 2 × 4 intraoperative grid successfully identified the precentral gyrus with tumor infiltration. However, the high negative predictive value of TMS tractography (97%) found in our previous study informed our intraoperative decision to carefully pursue a GTR while the patient underwent neuromonitoring.<sup>5</sup> The patient demonstrated mild transient postoperative weakness that resolved by her discharge 1 week later. This case is the first, to our knowledge, to demonstrate the safe resection of the precentral gyrus directly visualized intraoperatively by SSEPs.

Recent publications have demonstrated that gliomas can induce cortical neuroplasticity by exploiting the architecture of latent interneurons that facilitate healthy global connectivity.<sup>8,9</sup> Previous work from our group has shown evidence of this phenomenon by using TMS tractography to provide evidence of topographic displacement of cortical motor "hubs," supporting previous work by Duffau et al.<sup>8</sup> These hubs then seem to recruit new WMTs to send their specialized information, driving activity and subsequently increased fractional anisotropy (FA) of the new WMTs.<sup>5,9</sup> However, the old, latent WMTs presumably retain their original structural integrity and connection to the brain stem, spinal cord, and peripheral nerves.<sup>8</sup> Resection of these new cortical hubs and their connecting subcortical fibers predicts permanent deficits with an extremely high positive and negative predictive value.<sup>5</sup>

Accordingly, techniques that localize anatomical structures, such as structural MRI, anatomical tractography, or intraoperative SSEPs, may not reliably identify these new topographic representations of eloquence. Anatomical tractography outlines subcortical fibers that connect the precentral gyrus to the brain stem. Intraoperative SSEPs identify the central sulcus by recording the cortical sensory representation of a stimulus applied to the median nerve. The 2 × 4 grid localizes the difference in electrical potential (phase reversal) between afferent neurons (sensory cortex) and efferent neurons (motor cortex).<sup>7</sup> These techniques rely on the structural integrity of WMTs, which seemingly would not be affected by the previously described, clinically relevant glioma-induced neuroplasticity. This case provides anecdotal evidence to support this theory by demonstrating the safe resection of structures identified as eloquent by all three modalities: preoperative MRI, anatomical tractography, and intraoperative SSEPs.

While the patient's seizure risk precluded direct cortical stimulation, findings from this case could shed light on the technique's relationship with functional outcomes. Direct stimulation mechanically

associates with SSEPs, relying on the structural integrity of WMTs to propagate an exogenously applied electrical stimulus to the brain stem and spinal cord.<sup>10</sup> Accordingly, it remains unclear whether neuroplastic topographic displacement of cortical hubs compromises the ability of the previous, latent circuitry to successfully propagate the electrical stimulus.

Indirect empirical data may provide insight and direction for future work. Although preoperative TMS data strongly correlate with intraoperative stimulation for motor mapping, recent work from our institution showed the safe resection of a subset of TMS points.<sup>5</sup> Additionally, this case and others from our institution demonstrate the safe resection of white matter fibers identified by anatomical tractography, which also correlate well with intraoperative stimulation.<sup>11,12</sup> Finally, this case shows the safe resection of the anatomically defined primary motor cortex identified by SSEPs despite the strong association with direct stimulation, both mechanistically and empirically. Perhaps future research can reliably and reproducibly find subsets of direct cortical stimulation points that can be safely resected, allowing for consistent expansion of the extent of resection.

## Lessons

Correlating postoperative image analysis from this case with previous literature shed light on the potential clinical impact of our nontraditional surgical decisions. Fig. 1 shows what normal surgical boundaries would have been, using traditional anatomical and functional intraoperative modalities. This analysis indicated that a maximum of 45% resection would have been achieved, leaving about 17 cm<sup>3</sup> residual tumor. Marko et al.<sup>13</sup> published a landmark study directly correlating extent of resection with expected survival in patients with glioblastoma. Based on these data, performing a GTR instead of a 45% subtotal resection increased the expected survival from 200 days to 400 days. Another study correlated the volume of residual tumor with expected survival in patients with glioblastoma.<sup>14</sup> Using this data, the GTR that left the patient with no residual tumor instead of 17 cm<sup>3</sup> residual tumor increased expected survival from 10 months to 18 months. The striking similarities between different studies using different metrics seem to validate the conclusion that our alternative approach nearly doubled the expected survival of the patient.

The improved expected survival and sustained functional capacity for this patient illustrate the profound potential in optimizing presurgical imaging for patient selection, surgical planning, and intraoperative decisions. Complete neurological recovery within 1 week in this patient despite the aggressive resection provides further reason to reevaluate surgical decisions based on traditional preoperative planning and intraoperative mapping. In our view, scaling this work to impact more patients requires further utilization of pre- and postoperative overlays (perioperative overlays) correlated to clinical outcome both at an individual and aggregated level to definitively understand which cortical and subcortical brain structures are truly eloquent. Preliminary investigations using this technique have yielded vital information that led to this patient receiving a GTR that significantly improved her expected survival.

Traditional imaging as well as intraoperative mapping for this patient with a motor eloquent glioma indicated that only a 45% resection could be safely achieved. However, TMS tractography combined with previous data from our institution facilitated a GTR of conventionally eloquent anatomical structures while incurring no new neurological deficits. To optimize the onco-functional balance fully, future research should further explore the appropriate role of increasingly

sophisticated neuroimaging versus traditional structural imaging and conventional methods of intraoperative mapping.

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## 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: Muir, Traylor, Patel, Prabhu. Acquisition of data: Muir, Prinsloo, Ene, Tummala, Prabhu. Analysis and interpretation of data: Prabhu. Drafting the article: Muir, Ene, Prabhu. Critically revising the article: all authors. Reviewed submitted version of manuscript: Prinsloo, Traylor, Patel, Ene. Administrative/technical/material support: Prinsloo. Study supervision: Prabhu.

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