Personalized surgery of brain tumors in language areas: the role of preoperative brain mapping in patients not eligible for awake surgery

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OBJECTIVE Awake surgery represents the gold standard for resection of brain tumors close to the language network. However, in some cases patients may be considered not eligible for awake craniotomy. In these cases, a personalized brain mapping of the language network may be achieved by navigated transcranial magnetic stimulation (nTMS), which can guide resection in patients under general anesthesia. Here the authors describe their tailored nTMS-based strategy and analyze its impact on the extent of tumor resection (EOR) and language outcome in a series of patients not eligible for awake surgery.

METHODS The authors reviewed data from all patients harboring a brain tumor in or close to the language network who were considered not eligible for awake surgery and were operated on during asleep surgery between January 2017 and July 2022, under the intraoperative guidance of nTMS data. The authors analyzed the effectiveness of nTMS-based mapping data in relation to 1) the ability of the nTMS-based mapping to stratify patients according to surgical risks, 2) the occurrence of postoperative language deficits, and 3) the EOR.

RESULTS A total of 176 patients underwent preoperative nTMS cortical language mapping and nTMS-based tractography of language fascicles. According to the nTMS-based mapping, tumors in 115 patients (65.3%) were identified as true-eloquent tumors because of a close spatial relationship with the language network. Conversely, tumors in 61 patients (34.7%) for which the nTMS mapping disclosed a location at a safer distance from the network were identified as false-eloquent tumors. At 3 months postsurgery, a permanent language deficit was present in 13 patients (7.3%). In particular, a permanent deficit was observed in 12 of 115 patients (10.4%) with true-eloquent tumors and in 1 of 61 patients (1.6%) with false-eloquent lesions. With nTMS-based mapping, neurosurgeons were able to distinguish true-eloquent from false-eloquent tumors in a significant number of cases based on the occurrence of deficits at discharge (p < 0.0008) and after 3 months from surgery (OR 6.99, p = 0.03). Gross-total resection was achieved in 80.1% of patients overall and in 69.5% of patients with true-eloquent lesions and 100% of patients with false-eloquent tumors.

CONCLUSIONS nTMS-based mapping allows for reliable preoperative mapping of the language network that may be used to stratify patients according to surgical risks. nTMS-guided asleep surgery should be considered a good alternative for personalized preoperative brain mapping of the language network that may increase the possibility of safe and effective resection of brain tumors in the dominant hemisphere whenever awake mapping is not feasible.

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KEYWORDS brain tumors; navigated transcranial magnetic stimulation; tractography; brain mapping; language; awake surgery

AWAKE surgery represents the gold standard for resection of brain tumors located close to the language network.1 Performing surgery in awake patients improves the extent of tumor resection (EOR) as well as the postoperative language outcome of patients.1–4 The efficacy of this strategy is due to the increased possibility of achieving reliable, personalized, intraoperative mapping of the language network and monitoring of the language function during resection. The prompt identification of warning signs that occur in awake patients dur-
Here we report our experience using nTMS-based preoperative brain mapping for personalized reconstruction of the language network in a series of patients affected by language-eloquent brain tumors who were considered not eligible for awake surgery. We report the impact of our tailored nTMS-based strategy on the EOR and language outcome, with results suggesting that this strategy may be a good alternative for personalized preoperative brain mapping of the language network whenever awake surgery is not feasible.

**Methods**

**Patients**

We retrospectively reviewed data from all patients harboring a brain tumor close to the language network who underwent surgery at the Division of Neurosurgery of the University of Messina, Italy, between January 2017 and July 2022.

Inclusion criteria were as follows: patients aged ≥ 18 years harboring a brain tumor in the perisylvian region of the dominant hemisphere, for which awake surgery should be indicated, who underwent preoperative nTMS-based mapping and reconstruction of the language network and who were considered ineligible for awake surgery (noncollaborative, decreased mental capacity, anxiety, psychiatric disorders, refusing awake surgery).7-9,30,31

Exclusion criteria were age < 18 years, being eligible for awake surgery, and any contraindication for undergoing brain MRI and/or nTMS mapping (harboring an MRI-incompatible prosthesis, intractable seizures, etc.).18

All patients provided signed informed consent for the scientific use of their data according to the IRB at our institution.

**Preliminary Assessment of Language Eloquence of Tumors**

The preliminary suspected language eloquence of the tumors was defined by neurosurgeons on a standard brain MR image according to their location in the perisylvian region of the presumed dominant hemisphere. Then, neuropsychologists assessed the hemispheric dominance according to handedness using the Edinburgh Handedness Inventory.32 Once the suspected language eloquence of the tumor location was confirmed, all patients underwent the workup for preoperative nTMS-based mapping.

**Preoperative nTMS-Based Language Mapping**

All patients underwent preoperative nTMS language cortical mapping and nTMS-based tractography of subcortical fascicles for reconstruction of the language network and verification of the proximity of the tumor to the functional network.

Brain MRI using a 1.5-Tesla scanner (Achieva 1.5T, Philips Medical Systems) was performed for acquisition of the following sequences: 1) T1-weighted, gadolinium-enhanced multiplanar reconstruction (MPR) (TR = 8.1, TE = 3.7); 2) 3D FLAIR volumetric T2-weighted acquisition (TR = 8000, TE = 331.5/7); and 3) diffusion-weighted sequences (diffusion-weighted imaging [DWI]; TR = 2383.9, TE = 51.9) with 32 directions.
The T1-weighted MPR contrast-enhanced sequence—in case of enhancing lesions or the FLAIR sequence for nonenhancing lesions—was imported into the nTMS system (NBS system 4.3, Nexstim Oy). The nTMS language mapping was performed using repetitive stimulation as previously reported. Briefly, repetitive nTMS mapping was performed during the execution of an object-naming test. Repetitive stimulation consisted of trains of 5 pulses at 5 Hz using an intensity of 100% of the ipsilateral resting motor threshold that was previously computed. The repetitive stimulation over the cortical language critical sites induced different naming errors that were identified and classified (performance, semantic, or phonological errors) by the neuropsychologist at the end of nTMS mapping. Once naming errors had been classified, each cortical spot corresponding to the exact stimulation that elicited the error was identified and visualized over the 3D rendering of the patient’s brain MR image, thus representing the final nTMS cortical language mapping (Fig. 1). Finally, the cortical error spots were superimposed on the patient’s MR image and exported in DICOM format.

**nTMS-Based Tractography of Language Fascicles**

The patient MRI scan with the superimposed nTMS cortical error spots was imported with the DWI sequence into a planning station for the computation of the nTMS-based tractography of language fascicles (Fig. 2). All of the workflow for tractography was performed using StealthViz software (Medtronic Navigation) as previously described. Briefly, the nTMS cortical error spots were used as seeding regions of interest for the tractography of the arcuate fascicle (AF), inferior fronto-occipital fascicles (IFOFs), inferior longitudinal fascicle (ILF), uncinate fascicle (UF), and frontal aslant tract (FAT). The deterministic FACT (fiber assignment by continuous tracking) algorithm was used. The fractional anisotropy (FA) threshold was set to 0.20, the vector step length to 0.5 mm, the minimum fiber length to 30 mm, and the seed density to 1.0. The maximum directional change was 45° for the computation of the IFOF and ILF, and 90° for the AF, UF, and FAT.

**nTMS-Based Assessment of Language Eloquence and Evaluation of Awake Surgery Eligibility**

Once the nTMS-based tractography was computed, the 3D reconstruction of the whole language network was used to verify the spatial relationship between the tumor and the language network (Fig. 3). The language eloquence was then confirmed whenever the tumor was located at a distance ≤ 10 mm from the cortical nTMS language spots and/or the subcortical language tracts. In these cases, the tumor was defined as true eloquent, and surgery was considered to entail a high risk for postoperative permanent language deficits. Otherwise, tumors were considered false eloquent (Fig. 4). The reconstruction of the language network was used to plan a personalized surgical strategy and trajectory to achieve the maximal safe resection (Video 1).

**VIDEO 1. nTMS-based planning in a patient with a left temporal glioblastoma.** The nTMS spots are located around the tumor (orange) and are not overlapped with it. This finding may suggest false eloquence of the lesion, especially because the AF (green) and the UF (light red) are far away from the tumor. Conversely, the ILF (light blue) and IFOF (yellow) are very close to the medial portion of the tumor. The 3D reconstruction and visualization of the spatial relationship between the tumor and each component of the language network are presented. © Giovanni Raffa, published with permission. Click here to view.

Finally, the nTMS-based mapping data were exported to the neuronavigation system (StealthStation S8, Medtronic Navigation).

After the nTMS-based preoperative mapping, neuropsychologists were asked to verify the eligibility of the patient for awake surgery according to well-established criteria. Once the patient was defined as not eligible, asleep surgery was planned and performed.

**nTMS-Guided Resection of Tumors During Asleep Surgery**

Surgery was performed according to the individual patient’s personalized strategy based on the nTMS-based preoperative information. Furthermore, nTMS data were constantly available for visualization on the neuronavigation system to guide resection and preserve language-
eloquent structures (Fig. 5). Resection of pathological tissue infiltrating the nTMS-verified eloquent structures was avoided. Furthermore, removal of the tumor in the very proximity of the language network was performed slowly, layer by layer, and was stopped whenever the distance from the network was 5 mm. To increase the accuracy of navigation during these steps, superficial anatomical landmarks were established prior to the dural opening and continuously verified to correct the brain-shift distortion, especially at the latest stages of resection. In general terms, resection was stopped when gross-total resection (GTR) of the tumor had been achieved or whenever further tumor removal was considered not feasible because of the proximity/infiltration of the language network.

Outcome Analysis

The EOR was assessed on a postoperative early brain MRI scan (within 48 hours from surgery) as previously reported. The tumor volume was calculated by manual tumor segmentation across all the MRI slices by using the open-source Horos software (https://horosproject.org/). The EOR was defined as follows: GTR, no residual pathological tissue; subtotal resection (STR), < 10 ml of pathological tissue residue; partial resection, ≥ 10 ml of tissue residue.

Language performance was assessed by neuropsychologists using the Western Aphasia Battery (WAB) before surgery, at discharge, and after 3 months from surgery. The persistence of aphasia symptoms after 3 months from surgery was considered a permanent language deficit.

Finally, the accuracy of the nTMS-based preoperative mapping of the language network was assessed by analyzing its effectiveness in enabling neurosurgeons to predict postoperative permanent language deficits according to

FIG. 2. Example of nTMS-based tractography in a left temporal lobe tumor. A: Standard morphological T1-weighted contrast-enhanced sequence. B: nTMS-based tractography of each single language fascicle, including the AF (green), ILF (light blue), UF (red), and IFOF (yellow). C: Lateral (left) and craniocaudal (right) 3D views of the subcortical language fascicles, together with the nTMS spots (white) and the tumor (orange).
the preoperative stratification of tumors as true eloquent or false eloquent.

**Statistical Analysis**

The effectiveness of nTMS-based preoperative mapping for enabling neurosurgeons to stratify tumors as true eloquent versus false eloquent was analyzed by using Fisher’s exact test, computing the odds ratio, and analyzing sensitivity, specificity, and positive and negative predictive values. The outcome comparison in true-eloquent versus false-eloquent tumors and in patients with compared with those without preoperative deficits was performed by using Fisher’s exact test. Statistical significance was set at $p < 0.05$. Statistical analysis was performed by using GraphPad Prism version 9 for Mac (GraphPad Software Inc.).

**Results**

Data from 176 patients (99 male, 77 female; mean age 58.4 ± 16 years) who were not eligible for awake surgery and were operated on during asleep surgery were retrospectively collected and analyzed (Table 1). nTMS-based mapping was feasible in all patients. In 32 patients, the presence of peritumoral edema required a reduction of the FA threshold (in steps of 0.02, up to the inferior limit of 0.10) to achieve satisfactory nTMS-based tractography.

Of the 176 patients, 101 patients (57.4%) had high-grade gliomas, 31 (17.6%) had low-grade gliomas, and 23 (13.1%)

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**FIG. 3.** Example of the nTMS-based mapping and reconstruction in a case of a glioblastoma located in the left temporo-parieto-occipital junction. A: Standard morphological T1-weighted contrast-enhanced sequence. B: nTMS mapping shows error spots (white) located around the tumor. C: nTMS-based tractography shows the relationship between the AF (orange), ILF (light blue), UF (purple), IFOF (violet), and the tumor (yellow). D: The whole nTMS-based 3D reconstruction of the language network is used to analyze the relationship between the tumor and the network itself, in order to plan the safest tailored surgical strategy for resection.
FIG. 4. Case example of a left temporo-mesial diffuse astrocytoma considered true eloquent. The nTMS-based planning visualized in both 2D (upper box) and 3D (lower box) imaging showed that the lesion (red, indicated by the yellow arrow) was located deeply in relation to the vast majority of language fascicles.
FIG. 5. Example of the intraoperative use of the nTMS-based mapping information as guidance for resection in a case of a left temporal glioblastoma during the first stages of surgery (upper box), and in a case of a left glioblastoma in the temporo-parieto-occipital junction at the end of resection (lower box).
TABLE 1. Patient demographic characteristics and outcome data for surgery performed with nTMS-based preoperative mapping of tumors near language pathways (2017–2022)

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>176</td>
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</tr>
<tr>
<td>Mean age, yrs</td>
<td>58.4 ± 16</td>
<td>NA</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Male</td>
<td>99 (56.2)</td>
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</tr>
<tr>
<td>Female</td>
<td>77 (43.8)</td>
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<tr>
<td>Pathology</td>
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<tr>
<td>High-grade gliomas</td>
<td>101 (57.4)</td>
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<tr>
<td>Low-grade gliomas</td>
<td>31 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Metastases</td>
<td>23 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>21 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Preop deficits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True eloquent</td>
<td>35/115 (30.4)</td>
<td></td>
</tr>
<tr>
<td>False eloquent</td>
<td>6/61 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Postop deficits at discharge</td>
<td>27 (15.3)</td>
<td>&lt;0.0008</td>
</tr>
<tr>
<td>True eloquent</td>
<td>25/115 (21.7)</td>
<td></td>
</tr>
<tr>
<td>False eloquent</td>
<td>2/61 (3.2)</td>
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<tr>
<td>Permanent deficits at 3 mos postop</td>
<td>13 (7.3)</td>
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<tr>
<td>True eloquent</td>
<td>12/115 (10.4)</td>
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<tr>
<td>w/ preop deficit</td>
<td>10/35 (28.5)</td>
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<tr>
<td>w/o preop deficit</td>
<td>2/80 (2.5)</td>
<td></td>
</tr>
<tr>
<td>False eloquent</td>
<td>1/61 (1.6)</td>
<td></td>
</tr>
<tr>
<td>w/ preop deficit</td>
<td>0/6 (0)</td>
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<tr>
<td>w/o preop deficit</td>
<td>1/55 (1.8)</td>
<td></td>
</tr>
<tr>
<td>EOR</td>
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<tr>
<td>GTR</td>
<td>141 (80.1)</td>
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<td>True eloquent</td>
<td>80/115 (69.5)</td>
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<tr>
<td>False eloquent</td>
<td>61/61 (100)</td>
<td></td>
</tr>
<tr>
<td>STR</td>
<td>26 (14.8)</td>
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<tr>
<td>True eloquent</td>
<td>26/115 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Partial resection</td>
<td>9 (6.1)</td>
<td></td>
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<tr>
<td>True eloquent</td>
<td>9/115 (7.8)</td>
<td></td>
</tr>
<tr>
<td>GTR in pts w/ preop deficits</td>
<td>38/41 (92.6)</td>
<td>&lt;0.0001</td>
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<tr>
<td>True eloquent</td>
<td>32/35 (91.4)</td>
<td></td>
</tr>
<tr>
<td>False eloquent</td>
<td>6/6 (100)</td>
<td></td>
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<tr>
<td>GTR in pts w/o preop deficits</td>
<td>103/135 (76.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>True eloquent</td>
<td>48/80 (60)</td>
<td></td>
</tr>
<tr>
<td>False eloquent</td>
<td>55/55 (100)</td>
<td></td>
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</table>

NA = not applicable; pts = patients.
All data reported as number or number (%) of patients unless otherwise indicated. Mean values are presented with SDs.
* Includes mixed glioneuronal tumors, embryonal tumors, and hemangiomas.

had brain metastases. The remaining 21 patients (11.9%) were affected by other intrinsic neoplasms. Before surgery, 41 patients (23.3%) showed some impairment in language function as demonstrated by a reduced WAB score.

According to preoperative nTMS-based mapping, tumors in 115 patients (65.3%) were confirmed to be true-eloquent lesions because of a close spatial relationship with the language network. Conversely, in 61 patients (34.7%) nTMS mapping disclosed a larger and safer distance between the tumor and the language network than what was hypothesized on the basis of the standard MRI scan. These tumors were defined as false eloquent.

At discharge, worsening of the preoperative language performance was observed in 27 patients (15.3%). Among these patients, 25 had tumors that were preoperatively classified as true-eloquent tumors (25 of 115, 21.7%), and only 2 patients had tumors that were defined as false eloquent (2 of 61, 3.2%).

After 3 months postsurgery, permanent language deficits were still present in 13 patients (7.3%). According to the nTMS-based preoperative classification of language eloquence, a permanent deficit was observed in 12 of 115 patients (10.4%) with true-eloquent tumors, and in 1 of 61 patients (1.6%) with false-eloquent lesions, in whom an ischemic complication was documented after surgery.

The use of nTMS-based preoperative language mapping enabled the neurosurgeons to distinguish true-eloquent versus false-eloquent tumors in a significant number of patients, as verified by the occurrence of deficits at discharge (p < 0.0008) and after 3 months from surgery (p = 0.03). In the latter case, sensitivity was 92.3%, specificity was 36.8%, positive predictive value was 10.4%, and negative predictive value was 98.3% (OR 6.99, 95% CI 1.21–76.13).

In the overall study population, GTR was achieved in 141 patients (80.1%), STR in 26 (14.8%), and PTR in the remaining 9 patients (5.1%) (Fig. 6). However, GTR was achieved in all 61 cases of false-eloquent tumors (100%) and in 80 of 115 true-eloquent tumors (69.5%).

After co-registration of the postoperative MR scan with the preoperative data sets, including the nTMS-based reconstruction of the language network, permanent deficits were observed in 2 of 12 patients in whom resection involved subcortical language tracts (Fig. 7).

Discussion

Awake surgery represents the best personalized strategy for mapping and monitoring the language network during the resection of brain tumors in the dominant hemisphere. 1,2,4,44,45 Unlike the sensorimotor network, the language network is characterized by higher complexity and huge neuroplasticity potential that can be easily induced by the presence of a brain tumor. 6,34,46,47 Individually tailored intraoperative identification of the language network in each patient, including eventual modification induced by neuroplasticity, is mandatory to preserve the patient’s language performance. Such a goal can be achieved only through awake mapping of the language network. A recent meta-analysis demonstrated that with awake mapping postoperative permanent language deficits are reduced and EOR is increased in patients undergoing glioma surgery compared with patients who undergo resection under general anesthesia without the use of awake mapping of eloquent areas of the brain. 1

However, awake mapping requires high motivation and cooperation from patients. 36,48 Although no age limits have ever been defined for this procedure, awake mapping may not be feasible in younger or older patients who are unable
to collaborate during surgery. Moreover, some conditions, such as obstructive sleep apnea and difficult intubation, are considered absolute contraindications for awake surgery. Finally, psychiatric disorders, including severe anxiety disorders, mental confusion, inability to concentrate, and emotional instability, are usually considered exclusion criteria for a possible awake craniotomy. In these cases, forcing the awake mapping despite the presence of contraindications may result in a failed awake surgery.

A personalized surgical strategy for preserving the language network in patients considered not eligible for awake surgery has never been systematically described. In the era of personalized medicine, standard asleep surgery is not the only alternative to awake mapping in these patients. In this study, we investigated a novel strategy for preoperative “personalized” mapping of the language network based on repetitive nTMS language mapping and nTMS-based tractography.

Several studies have demonstrated a good correlation between repetitive nTMS mapping of language cortical areas and findings from intraoperative direct electrical stimulation (DES). A recent meta-analysis confirmed the accuracy of nTMS language mapping in all included studies, with low total numbers of false-negative nTMS results in mapped areas, especially in the anterior language areas.

In addition, nTMS-based diffusion tensor imaging (DTI) tractography provides a reliable reconstruction of the language network. Tuncer et al. demonstrated that nTMS-based tractography of language pathways provides a tailored reconstruction that can help neurosurgeons determine the individual aphasia risk profile in each patient. Sollmann et al. reported that the risk of developing postoperative permanent language deficits was significantly higher when the nTMS-based reconstruction of the language network showed a distance of the tumor < 7 mm from the AF or ≤ 10 mm from other language fascicles.

In our larger series, using a distance cutoff value of 10 mm, we confirmed the successful use of nTMS-based reconstruction of the language network to distinguish between true-eloquent lesions—with a significantly higher risk of postoperative permanent deficits—and false-eloquent lesions. In particular, the observed high negative predictive value (98.3%) confirmed that nTMS-based mapping

**FIG. 6.** Case example of left temporal glioblastoma. A: Standard morphological T1-weighted contrast-enhanced MRI sequence. B: nTMS mapping shows error spots (white) located just posteriorly to the tumor. C: nTMS-based tractography shows the relationship between the AF (green), ILF (light blue), UF (pink), IFOF (red), and the tumor (yellow). D: The whole nTMS-based 3D reconstruction of the language network shows that all fascicles are located medially to the tumor. E: Postoperative T1-weighted contrast-enhanced sequence showing GTR of the tumor.
is particularly effective for predicting the false eloquence of lesions, which may be useful in patients not eligible for awake mapping by indicating a lower risk of developing postoperative permanent deficits, thus inducing neurosurgeons to perform a more aggressive resection.

However, the reported studies in the current literature are mainly series in which the nTMS-based mapping was used only as an adjunctive tool for preoperative planning in patients prior to awake intraoperative mapping. Only a few case series have been reported that investigated the use of this strategy as a guide for resection in patients prior to asleep surgery.\textsuperscript{6,15,30,53} Hendrix et al. analyzed the occurrence of postoperative language deficits and the EOR in a series of 20 patients who underwent preoperative nTMS language mapping and were then operated on while under general anesthesia.\textsuperscript{30} Hendrix et al. compared their findings with those from a matched historical control group of 20 patients who were operated on without preoperative nTMS mapping; these authors reported a significantly improved language outcome at 6 weeks from surgery in the nTMS group and a GTR rate of 65% in both groups. The largest study on the topic to date was performed by Ille et al. in a series of 100 patients who underwent asleep surgery.\textsuperscript{53} Ille et al. compared the findings in the nTMS group with the results from 47 patients operated on during awake surgery. These authors reported no significant differences regarding language outcomes and GTR rates in patients with preoperative nTMS language mapping who underwent asleep surgery and those who underwent awake surgery. In particular, the occurrence of permanent deficits and GTR rates were, respectively, 5.6% and 83.3% in the nTMS group versus 7.5% and

\begin{figure}[h]
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\caption{The upper row shows a case example of a patient operated on for a left temporal glioblastoma who showed a permanent language deficit: A: Co-registration of the postoperative T2-weighted sequence with preoperative data set shows that the resection cavity involves the inferior trunk of the UF (pink, indicated by the red arrow); conversely, the cortical area corresponding to a close nTMS spot has been preserved (green arrow). B: T1-weighted contrast-enhanced preoperative MR image. C: A 3D reconstruction of the language network showed that the UF was already infiltrated by the tumor (yellow) before surgery (red arrow). The bottom row shows the case of a glioblastoma located in the left temporo-parieto-occipital junction in a patient who did not develop a postoperative language deficit: D: Preoperative nTMS-based mapping shows the lesion is close to the main trunk of the AF (orange, indicated by the white arrow). E and F: After co-registration with the preoperative nTMS-based data, the postoperative MR scan shows GTR of the tumor and preservation of the brain parenchyma corresponding to the AF (white arrow) in the axial (E) and sagittal (F) planes. CST = corticospinal tract.}
\end{figure}
Finally, brain shift is another important limitation affecting the intraoperative use of nTMS data for navigation, especially at the latest stages of resection. We tried to reduce surgical inaccuracy associated with brain shift by performing continuous verification of established superficial anatomical landmarks during surgical navigation; however, brain shift was responsible for the unintended resection of subcortical tracts in 2 patients.

Conclusions
Awake surgery is still the most effective personalized surgical strategy for mapping the language network, preserving it, and achieving the maximal safe resection of brain tumors in the dominant hemisphere. However, in patients not eligible for awake surgery, nTMS-based mapping and reconstruction of the language network is a valid alternative for performing tailored preoperative mapping of the network that may guide neurosurgeons to achieve personalized, safe, and effective resection of brain tumors in patients under general anesthesia.

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References

Study Limitations
The retrospective design represents the most important limitation of this study. However, we were able to describe findings from what is, to our knowledge, the largest series ever reported using nTMS-based preoperative mapping for resection of language-eloquent tumors in patients under general anesthesia and compare the outcomes in these patients with outcomes reported for similar patients in the most up-to-date literature on the topic.

Another limitation of the present study, in common with reported studies on awake surgery, is the impossibility of performing preoperative nTMS mapping in patients with severe language deficits. Also, nTMS-based tractography may be negatively influenced in cases of severe peritumoral edema.

70% in the awake surgery group. In our series, we recorded an overall occurrence of permanent language deficits in 7.3% of patients. This percentage increased to 10.4% when considering only true-eloquent tumors disclosed by preoperative nTMS mapping. On the other hand, the percentage of permanent language deficits was only 1.6% in false-eloquent tumors. Regarding the EOR, we found an overall GTR rate of 80.1%, and when we stratified patients according to nTMS mapping, GTR was obtained in 69.5% of patients with true-eloquent tumors and in 100% of patients with false-eloquent lesions. Therefore, our overall findings are not so different from those reported in previous studies. However, we were also able to preoperatively stratify patients according to their surgical risk based on nTMS mapping.

In the literature, results regarding the incidence of postoperative language deficits and the achieved GTR rate after awake mapping are very inhomogeneous. In case-control studies comparing patients undergoing awake and asleep surgery, the occurrence of permanent deficits (still present >3 months postoperatively) varies from 0% to 18.2% and the GTR rate from 21.6% to 100%. However, different results have been reported for single-center studies of large series. In survivors 3 months after awake surgery, Sanai et al. reported new language deficits in 2.4% and a GTR rate of 59.6%. Conversely, Clavreul et al. reported the occurrence of permanent language deficits in 21.7% of cases and a GTR rate of 61%. Our results regarding the EOR do not differ significantly from those reported in the literature. However, when considering findings regarding the occurrence of new postoperative permanent deficits, it must be emphasized that all studies in which a preoperative evaluation of the spatial relationship between the tumor and the language network is based only on the experience of the neurosurgeon in the evaluation of the standard morphological MRI scan—and not on functional examinations such as nTMS mapping or functional MRI—suffer from a kind of “selection bias” during patient enrollment. This bias, which may explain the very low reported incidence of new language deficits in some series, is attributable to the inclusion of an unknown number of patients with false-eloquent tumors who are at low risk for developing postoperative permanent deficits and is also documented by the frequent occurrence of negative mapping results during awake surgery.


45. Duffau H, Peggy Gatignol ST, Mandonnet E, Capelle L, Tail-


Disclosures
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Author Contributions
Conception and design: Raffa. Acquisition of data: Marzano, Raffa, Curcio, Espahbodine. Analysis and interpretation of data: Raffa, Curcio, Espahbodine. Drafting the article: Raffa, Curcio, Espahbodine. Critically revising the article: Raffa, Germanò, Angileri. Reviewed submitted version of manuscript: Raffa, Germanò. Approved the final version of the manuscript on behalf of all authors: Marzano. Statistical analysis: Raffa, Curcio. Study supervision: Raffa, Germanò.

Supplemental Information
Videos

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