Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients

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Object. Although a growing number of authors currently advocate surgery to treat low-grade gliomas, controversy still persists, especially because of the risk of inducing neurological sequelae when the tumor is located within eloquent brain areas. Many researchers performing preoperative neurofunctional imaging and intraoperative electrophysiological methods have recently reported on the usefulness of cortical functional mapping. Despite the frequent involvement of subcortical structures by these gliomas, very few investigators have specifically raised the subject of fiber tracking. The authors in this report describe the importance of mapping cortical and subcortical functional regions by using intraoperative real-time direct electrical stimulations during resection of low-grade gliomas.

Methods. Between 1996 and 2001, 103 patients harboring a corticosubcortical low-grade glioma in an eloquent area, with no or only mild deficit, had undergone surgery during which intraoperative electrical mapping of functional cortical sites and subcortical pathways was performed throughout the procedure.

Both eloquent cortical areas and corresponding white fibers were systematically detected and preserved, thus defining the resection boundaries. Despite an 80% rate of immediate postoperative neurological worsening, 94% of patients recovered their preoperative status within 3 months—10% even improved—and then returned to a normal socioprofessional life. Eighty percent of resections were classified as total or subtotal based on control magnetic resonance images.

Conclusions. The use of functional mapping of the white matter together with cortical mapping allowed the authors to optimize the benefit/risk ratio of surgery of low-grade glioma invading eloquent regions. Given that preoperative fiber tracking with the aid of neuroimaging is not yet validated, we used intraoperative real-time cortical and subcortical stimulations as a valuable adjunct to the other mapping methods.

Key Words • subcortical mapping • low-grade glioma • surgery • sensorimotor cortex

Despite published opinions favoring surgery for low-grade gliomas, controversy still persists, especially because of the risk of inducing permanent neurological deficit if the tumor is located near or within so-called eloquent brain areas. Many researchers performing preoperative neurofunctional imaging and intraoperative electrophysiological methods have recently reported on the usefulness of cortical functional mapping. Despite the frequent involvement of subcortical structures by these gliomas, very few investigators have specifically raised the subject of fiber tracking. The authors in this report describe the importance of mapping cortical and subcortical functional regions by using intraoperative real-time direct electrical stimulations during resection of low-grade gliomas.

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As a rule, low-grade gliomas invade cortical as well as subcortical structures, and thus definitive deficits may occur because of surgical damage to pathways running in the white matter.

Currently, we present a consecutive series of 103 patients who, during an operation for a low-grade glioma located in eloquent corticosubcortical areas, underwent real-time mapping of both sensorimotor and language cortical sites and white fibers. Throughout these surgeries we performed direct electrical stimulations as described by Berger and colleagues. Clearly, the aim of our work was not to study the impact of surgery on the natural history of a low-grade glioma, but rather to detail both immediate and delayed postoperative functional results after performing a maximal resection according to functional boundaries determined with the aid of intraoperative cortical and subcortical map-

Abbreviations used in this paper: DW = diffusion-weighted; fMR = functional magnetic resonance; KPS = Karnofsky Performance Scale; PET = positron emission tomography; SSEP = somatosensory evoked potential.
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plings. After collecting these data, we reviewed the literature on tumor surgery in eloquent areas, with particular focus on technical and functional considerations.

Clinical Material and Methods

Between October 1996 and October 2001, 103 patients underwent surgery for a corticosubcortical low-grade glioma located in eloquent brain areas with the aid of intraoperative electrical mapping. Note that part of this experience has been previously described, in particular, the anatomofunctional organization of the language pathways but not the detailed data regarding neurological outcome.

The presenting symptoms and results of the preoperative neurological examination were assessed by both the neurologists (D.D. and L.T.) and neurosurgeons (H.D., L.C., M.L., A.B., J.P.S., and R.V.E.). The intensity of the motor deficit was rated using a standardized motor scale as follows: 0, no deficit; 1, mild deficit (patient can use his or her limb almost normally, that is, walking is possible, but there is impairment of fine movements of the upper limb); 2, moderate deficit (movement is possible with help from the examiner); and 3, severe deficit (no spontaneous movement against gravity). Speech functions were evaluated clinically by neurologists, neurosurgeons, and/or a speech therapist (P.G.), who tested verbal comprehension, spontaneous speech, naming, verbal fluency, narrative tasks, and repetition. Moreover, a neuropsychological task performed by the patient was assessed in the second half of the series (that is, 1998) by a neuropsychologist (N.S.). Finally, we evaluated the patient's score for each such task.

Hemispheric dominance was defined using a standardized questionnaire and fMR images obtained while the patient performed semantic-fluency, covert sentence-repetition, and story-listening tasks. Data were analyzed with the aid of pixel-by-pixel autocorrelation and cross-correlation. The fMR imaging laterality indices were defined for several regions of interest as the ratio (L – R)/(L + R), where L is the number of activated voxels in the left hemisphere and R is that in the right hemisphere.

The topography of the tumor was accurately demonstrated on preoperative MR images (T1-weighted and spoiled-gradient images obtained before and after Gd enhancement in the three orthogonal planes, T2-weighted axial images, and fluid-attenuated inversion recovery axial images in the last 3 years of the study). During all surgical procedures, intraoperative real-time functional corticosubcortical mapping was performed—motor mapping in 39 patients after induction of general anesthesia, and somatosensoric and language mappings in 64 patients after administration of a local anesthetic agent—using the technique of direct electrical stimulations, previously detailed by us, and based on the methodology of Berger and colleagues. The aim of this study was to track and preserve eloquent structures during each moment and at each site of resection. Language tasks included the performance of systematic counting, naming, and reading. Moreover, a calculation task was added if a patient harbored a lesion in the left angular and supramarginalis gyri, and repetition and/or semantic tasks were added if a patient had a tumor within the left mid-posterior temporal lobe. Briefly, bipolar electrode tips spaced 5 mm apart and delivering a biphasic current (pulse frequency 60 Hz, single-pulse phase duration 1 msec, and amplitude 6–18 mA [general anesthesia] or 2–6 mA [local anesthesia]) (Ojemann cortical stimulator 1; Radionics, Inc., Burlington, MA) were applied to the patient’s brain. First, before tumor removal, electrical mapping was completed at the cortical level to identify the essential eloquent sites that needed to be avoided and thus to define the superficial boundaries of resection according to functional data. To define the intensity of the current, we progressively increased the amplitude until a clinical motor response was obtained (after general or local anesthesia had been induced). We then used this intensity to perform somatosensory and language mappings after a local anesthetic agent had been administered, without monitoring after-discharge activity.

Second, direct stimulations, with the same electrical parameters as those used at the cortical level, were continuously applied during glioma removal at the subcortical level to detect somatosensoric and/or language pathways, which represented the deep functional limits of resection.

With the patient in a state of general anesthesia, subcortical stimulations were applied continuously to avoid interruption of the pyramidal fibers between the two brain stimulation trials. Despite repetitive stimulations, there was no consideration of the eloquent structures until motor pathways were encountered, that is, until a motor response was induced. Tumor removal was stopped once movement was elicited, and the same procedure was performed again in neighboring regions by closely following the corticospinal tracts with subcortical stimulations.

After having administered a local anesthetic and throughout the entire glioma removal procedure, the patient was asked to perform tasks continuously, including motor opening and closing of the hand with the superior limb raised (with or without regular movements of the foot) as well as language tasks. Most of the time, these tests were controlled by the speech therapist (P.G.) or neuropsychologist (N.S.) or, more rarely, by the anesthesiology team, the members of which had been trained in language testing (M.C.M., S.R., and J.C.M.) and had received standardized instructions detailed by the speech therapist. As soon as the slightest limb weakness and/or dysphasia was noted, resection was stopped and subcortical stimulation was applied to check for any involuntary motor response and/or a speech disturbance. If either of these occurred, glioma removal was interrupted at this site, and the same procedure was again performed in the neighboring structures. If neither occurred, the patient was asked to rest, and when the tasks were normalized several minutes later, resection was resumed under the same conditions. In the case of parietal low-grade gliomas, subcortical stimulations were performed so that the awake patient could signal the induction of paresthesia, which would indicate that the resection had to cease because thalamocortical pathways had been encountered.

At the end of the resection procedure, the integrity of the functional networks was systematically verified. With the patient in a state of general anesthesia, we stimulated the motor cortical sites. If the movements elicited were the same as those evoked before tumor removal, the motor pathways were considered to be intact, thus meaning that the patient would recover despite the possibility of incurring an immediate postoperative deficit. Again after in-
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<td>fronto-precentral region</td>
<td>40</td>
<td>seizures (39 [8 PRE]), ICH (1)</td>
<td>normal (36), motor deficit (2), speech deficit (2)</td>
<td>100 (28), 90 (3), 80 (9)</td>
<td>posteriorly, pyramidal pathways (all cases); dominant hemisphere: medially, fasciculus subcallosal medialis w/o or w/o head of caudate nucleus; more laterally, language pathways from premotor cortex; again more laterally, language pathways from the Broca area deeply, pyramidal pathways within internal capsule; dominant hemisphere: deeply, arcuate fasciculus within external capsule w/o or w/o lat part of putamen</td>
<td>normal (5), slight deficit (12), moderate deficit (12), severe deficit (11)</td>
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</tr>
<tr>
<td>F1 28 (8 rt, 20 lt)</td>
<td>normal (27), speech deficit (2)</td>
<td>100 (11), 90 (5), 80 (13)</td>
<td>normal (5), slight deficit (13), moderate deficit (4), severe deficit (7)</td>
<td>100 (6), 90 (16), 80 (4), 70 (3)</td>
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<td>normal (9), speech deficit (1)</td>
<td>100 (8), 80 (2)</td>
<td>normal (4), slight deficit (4), moderate deficit (1), severe deficit (1)</td>
<td>100 (7), 90 (2), 80 (1)</td>
<td>temporo-parietal part of arcuate fasciculus (anterior-middletemporal glioma)</td>
<td>normal (9), slight deficit (5), moderate deficit (1)</td>
<td>4 T, 4 ST, 1 P</td>
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<td>F3 7 (4 rt, 3 lt)</td>
<td>normal (9)</td>
<td>100 (9)</td>
<td>deeply, posterosuperior loop of arcuate fasciculus; more superficially, locoregional language connections</td>
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<td>parieto-temporal junction (dominant hemisphere)</td>
<td>9 (9 lt)</td>
<td>seizures (9)</td>
<td>normal (9)</td>
<td>normal (3), slight deficit (5), moderate deficit (1)</td>
<td>100 (7), 90 (2), 80 (1)</td>
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<tr>
<td>rolandoic region</td>
<td>8 (6 rt, 2 lt)</td>
<td>seizures (8 [2 PRE])</td>
<td>normal (7), motor deficit (1)</td>
<td>100 (5), 80 (3)</td>
<td>anteriorly, pyramidal pathways; posteriorly, somatosensory thalamocortical pathways; dominant hemisphere: laterally, language pathways coming from ventral premotor &amp; facial primary motor cortices</td>
<td>normal (3), slight deficit (3), moderate deficit (1), severe deficit (1)</td>
<td>normal (7), motor deficit (1)</td>
<td>100 (4), 90 (3), 70 (1)</td>
<td>2 T, 4 ST, 2 P</td>
</tr>
<tr>
<td>parieto-striatal region</td>
<td>7 (4 rt, 3 lt)</td>
<td>seizures (6), ICH (1)</td>
<td>normal (5), hyp-esthesia (2)</td>
<td>100 (5), 80 (2)</td>
<td>anteriorly, somatosensory thalamocortical pathways (all cases); dominant hemisphere: anteriorly (deeply), language pathways issued from supramarginalis gyrus &amp; joined the posterosuperior part of arcuate fasciculus</td>
<td>normal (2), slight deficit (4), moderate deficit (1)</td>
<td>normal (7)</td>
<td>100 (4), 90 (3), 3 P</td>
<td>2 T, 2 ST, 3 P</td>
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</table>

* F1 = superior frontal gyrus; F2 = middle frontal gyrus; F3 = inferior frontal gyrus; ICH = intracranial hypertension; P = partial; PRE = pharmacologically resistant epilepsy; ST = subtotal; T = total.
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duction of local anesthesia, we asked the patient to repeat all functional tasks. The absence of a deficit meant that the patient would recover despite an eventual immediate postoperative sensorimotor and/or language disorder.\textsuperscript{36,43} Intraoperative glioma delineation was systematically determined using ultrasonography or neuronavigation.

All patients were examined in the immediate postoperative period, at 3 months, and then every 6 months thereafter, by the same team of neurosurgeon, neurologist, and neuropsychologist, who had assessed the same tasks performed preoperatively. A control MR image was obtained in all cases immediately, 3 months, and then every 6 months postsurgery, to evaluate the quality of glioma removal according to the classification method reported on by Berger and colleagues\textsuperscript{8} (that is, total resection indicated no residual signal abnormality, subtotal resection indicated $< 10 \text{ cm}^3$ of residue, and partial resection indicated $> 10 \text{ cm}^3$ of residue). All MR images were systematically interpreted by at least two observers.

Patient Population

This series included 48 men and 55 women, ranging in age from 17 to 63 years (mean 36 years). All but four patients were right handed. Presenting symptoms included seizures in 95% of cases and intracranial hypertension in 5%. Pharmacologically resistant epilepsy was present in 27 patients. Results of an initial detailed neurological examination were normal in all patients except 10 who presented with a mild motor deficit (rated 1 on the standardized motor scale; three patients), a slight hysteresis (two patients), and a reduction in verbal fluency (five patients). Twenty-nine patients had a KPS score of 80, eight patients a score of 90 (able to work despite a mild deficit and/or chronic seizures), and 66 a score of 100. In patients who underwent a preoperative neuropsychological evaluation, although results of the Mini-Mental State Examination were higher than 28, all displayed slight working memory disorders.

Preoperative MR Imaging

According to results of MR imaging, lesion locations were distributed as follows. Forty lesions were situated in the frontoprecentral region: 28 within the superior frontal gyrus, with involvement of the supplementary motor area (eight on the right side and 20 on the left); five in the middle frontal gyrus (one on the right side and four on the left); and seven in the inferior frontal gyrus (four on the right and three on the left). Twenty-nine lesions were located in the paralimbic region, with involvement of the insular lobe, and with or without the frontobasal and/or tempopolar regions (20 on the right and nine on the left). Ten gliomas were situated in the temporal area, with involvement of the dominant lobe (two on the right and eight on the left). Nine gliomas involved the left dominant parietooccipitotemporal junction. There were eight lesions in the Rolandic region (six on the right and two on the left), and seven in the parieto-occipitotemporal area (four on the right and three on the left).

Results

The clinical, radiological, and surgical data of the 103 patients are summarized in Table 1.

Surgical Findings

The initial cortical mapping allowed for the detection of eloquent areas, which were then used as boundaries of resection. The electrical subcortical mapping equally allowed for the direct identification and preservation of the functional fibers.

Low-Grade Gliomas in the Frontoprecentral Region. The posterior limit of resection for lesions in the frontoprecentral region was defined by the identification of the corticospinal pathways in all patients, for example, from medial to lateral directions, the motor tracts of the lower limb, upper limb, and face. Thus, the entire corona radiata could be identified, from the cortical surface to its junction with the internal capsule, at the level of the rotation of the fibers (Fig. 1).

Moreover, in the dominant hemisphere, resection boundaries were defined by language pathways (Fig. 2): medially, the fasciculus subcallosus medialis, from the supplementary motor area and cingulum to the head of the caudate nucleus, and from which were elicited transient symptoms of transcortical motor aphasia on stimulation (it was used as the medial limit of resection in cases of lesions invading the middle [with or without the inferior] frontal gyrus [four patients]); more laterally, the language fibers coming from the premotor cortex, and from which anoma and/or anarthria was induced on stimulation (it was used as the lateral limit of resection for lesions invading the superior frontal gyrus [20 patients] and as the medial boundary for tumors involving the inferior frontal gyrus [three patients]); again more laterally, the language fibers coming from the Broca area and connecting this region to the insula and primary motor cortex, from which was elicited speech arrest on stimulation (it was used as the lateral boundary of resection for low-grade gliomas involving the middle [with or without the superior] frontal gyrus [four patients]).

Low-Grade Gliomas in the Paralimbic Region. In the non-dominant hemisphere in 20 patients, the depth of resection was limited by the identification of the corticospinal pathways in the posterior limb of the internal capsule (with or without its junction with the corona radiata for lesions in the frontoinsular region, and its junction with the cerebral peduncles for tumors in the temporoinsular region). No motor response was induced by stimulation of the basal ganglia, thus allowing for resection (at least partially) of invading gliomas in 16 patients.

In the dominant hemisphere, after resection of at least part of the glioma in the insular area, the deep boundary was determined by the external capsule in which runs the arcuate fasciculus (eliciting paraphasia on stimulation). In one case the depth of resection was limited by the lateral part of the putamen more anteriorly (inducing anarthria when stimulated; Fig 3). Gliomas located in the left basal ganglia were never resected.

Low-Grade Gliomas in the Temporal Region. For anterior temporal low-grade gliomas in four patients, the posterior limit of resection limited by the identification of the language pathways running from the cortical language sites to the anterior brachium of the temporal part of the arcuate fasciculus (eliciting anoma or paraphasia when stimulated). For low-grade gliomas of the midtemporal region (four patients), the anterior limit of resection was represented by
the language pathways constituting the anterior brachium of the arcuate fasciculus, and the posterior limit was indicated by the language pathways constituting the posterior brachium of the arcuate fasciculus (Fig. 4). Moreover, above the ventricle, the posterosuperior boundary of resection may be represented by the pyramidal pathways within the internal capsule. In two patients with posterior temporal low-grade gliomas, the depth of resection was limited by the language pathways converging from the cortical sites to the posterior brachium of the temporal part of the arcuate fasciculus.

Low-Grade Gliomas of the Left Parietooccipitotemporal Region. The depth of resection for gliomas of the left parietooccipitotemporal region was limited by the identification of language pathways represented by the posterosuperior loop of the arcuate fasciculus and, more superficially, by locoregional connections between cortical language sites.
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Low-Grade Gliomas of the Rolandic Area. After detecting primary motor and/or somatosensory cortical sites, the sensorimotor pathways were followed closely, indicating the functional limits of glioma resection in the Rolandic region. Moreover, in the dominant hemisphere in two patients, language pathways coming from the primary motor area of the face and running to the frontal horn of the lateral ventricle behind the subcallosal fasciculus were identified by the induction of anarthria on stimulation.

Low-Grade Gliomas of the Parietoretrocentral Region. The anterior limit of resection for gliomas of the parietoretrocentral region was defined by the thalamocortical pathways, with identification of their somatotopic organization from the lateral horn of the ventricle to corresponding somatosensory cortical sites (for example, from medial to lateral directions, the sensory tracts of the inferior limb, superior limb, and face). In the dominant hemisphere in three patients, the depth of the anterolateral limit was represented.
by deep language pathways, which on stimulation most often elicited time anoma and/or paraphasia.

In summary, the surgical strategy in all cases was modulated according to subcortical mapping results, with the most extensive resection possible performed in 103 patients. Resection was never interrupted before the functional fibers were encountered, but was stopped as soon as these pathways were identified using subcortical stimulations.

During operations performed in patients in a state of general anesthesia, repetition of the cortical stimulations used to check the integrity of pyramidal pathways elicited the same motor response at the end of resection compared with responses elicited before resection in all patients except five; no movement was induced in three patients with a glioma in the right frontotemporinsular region and a major decrease in the motor response occurred in two patients with a right frontoprecentral lesion despite the use of the same electrical parameters (both had presented with a preoperative motor deficit). For surgeries performed after the administration of a local anesthetic, all patients except one remained able to perform motor and language tasks following resection; speech became impossible in a patient with a left precentral low-grade glioma, who had presented with preoperative language disturbances.

The median length of surgery was approximately 5 hours. Patients were awake, but the effects of the local anesthetic remained for a median 2 hours. With the use of a local anesthetic, the patients tolerated the procedure well. Despite their fatigue at the end of the resection procedure, many patients commented that they were relieved to help in the monitoring of their own neurological condition during glioma removal, and that if another operation was necessary in the future they would agree to undergo surgery again while awake.

**Clinical Results**

There was no operative or postoperative mortality.

**Immediate Postoperative Functional Results**

Eighty-one patients experienced neurological worsening immediately following the surgical procedure. Forty-one of these patients had a mild motor deficit (rated 1 on the standardized motor scale) and/or slight language disturbances (essentially a mild reduction in spontaneous speech). The median length of their hospital stay was approximately 5 to 7 days, and each patient underwent rehabilitation therapy at home. Twenty patients had a moderate motor deficit (rated 2) and/or moderate language disturbances (that is, a reduction in spontaneous speech, dysarthria, dysnomia, and impairment in verbal fluency, with no verbal comprehension disorder). The median duration of hospitalization in this subgroup was between 10 and 14 days, and these patients required a more intensive and prolonged rehabilitation therapy (3 months) at home. Twenty patients had a severe deficit (rated 3) and/or complete aphasia (most often due to a supplementary motor area syndrome or the aftermath of a frontotemporinsular glioma resection). A transfer to a rehabilitation center for at least 1 month was necessary in these cases.

**Delayed Postoperative Functional Results**

On examination at 3 months after surgery, eight patients had a mild deficit (motor scale rating of 1 and/or slight retardation of spontaneous speech) and 89 patients had normal neurological function. At this time, only a few patients had returned to a normal professional life (< 20%). A total of six patients maintained a severe deficit (motor scale rating of 3 in five cases and dysphasia in one case). At 9 months postsurgery, 97 patients had returned to a normal socioprofessional life. The KPS score was 80 in eight patients, 90 in 44, and 100 in 45. During the neuropsychological examination, results on a Mini-Mental State Examination were greater than 28 in all cases and preoperative working memory disorders slightly improved in 15% of cases (as shown by a higher score in the reversal order task).
The six patients with sequelae did become independent, but were unable to work normally, having a KPS score of 70.

In summary, in comparison with their preoperative status (Table 2), 10 patients had improved neurological functioning (from deficit and/or intracranial hypertension), and 19 of 27 patients who had presented with preoperative chronic epilepsy had improved functioning (11 patients had Engel Grade I). Ninety-seven of 103 patients returned to a normal life. The neurological functioning in six patients was permanently worsened—three with a right frontotemporalinsular low-grade glioma due to a deep ischemia involving the internal capsule (lenticulostriate artery damage, despite the preservation of the pyramidal pathways) and another three with a widely infiltrative frontocentral low-grade glioma, who had presented with a preoperative deficit.

Note that there was no difference in surgical methodology among the subgroups of patients with or without postoperative worsening of neurological functioning; that is, all resections were stopped based on cortical and subcortical mapping findings.

**Histological Results**

Results of the histopathological examination revealed a low-grade glioma (World Health Organization Grade II) in all cases.

**Radiological Results**

Thirty-one resections were defined as total (with no residual signal abnormality on MR imaging), 51 as subtotal

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<td>Preop Neurological Abnormalities (no. of patients)</td>
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<td>ICH (3)</td>
<td>slight deficit (41)</td>
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<tr>
<td>deficit (8)</td>
<td>moderate deficit (20)</td>
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<td>deficit &amp; ICH (2)</td>
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(< 10 cm³ of signal abnormality [there was < 5 cm³ in 23 cases]), and 21 as partial. There was no difference in surgical methodology among the subgroups of patients who had undergone total or incomplete removal, again because all resections were limited based on cortical and subcortical mapping findings.

Discussion

Although recent literature demonstrates a positive impact of surgery on the natural history of a low-grade glioma, controversy persists, mainly because of the risk of inducing neurological sequelae, especially when the glioma is located in eloquent brain areas. Permanent deficit rates between 13 and 20% have been reported in several studies.

Nonetheless, technical developments in functional mapping methods in the last decade have allowed for improvements in surgical strategies and thus postoperative outcome. First, the use of preoperative noninvasive methods of functional neuroimaging (PET scanning, fMR imaging, and magnetoencephalography) allows one to estimate the location of cortical eloquent areas in relation to the glioma, thus enabling one to plan the best surgical approach and limits of resection to avoid functional cortex. Second, image-guided surgery allows the neurosurgeon to benefit from individual anatomical data as well as the incorporation of preoperative functional neuroimaging in the neuronavigational system. Third, recording of evoked potentials during surgery is widely described for lesions located within the central region, to identify the Rolandic sulcus to avoid sensorimotor deficits. Fourth, the use of electrical cortical stimulations in patients in whom either general or local anesthesia has been induced is advocated to identify eloquent areas intraoperatively. Third, recording of evoked potentials during surgery is widely described for lesions located within the central region, to identify the Rolandic sulcus to avoid sensorimotor deficits. Fourth, the use of electrical cortical stimulations in patients in whom either general or local anesthesia has been induced is advocated to identify eloquent areas intraoperatively. Second, image-guided surgery allows the neurosurgeon to benefit from individual anatomical data as well as the incorporation of preoperative functional neuroimaging in the neuronavigational system.

Despite improvements in postoperative functional results by using these mapping methods, the identification and preservation of eloquent pathways within the white matter remains problematic. This issue is particularly acute in surgery for low-grade gliomas, because this kind of tumor most often involves cortical and subcortical structures and, moreover, shows an infiltrative progression along the white fibers. Thus, we report on the usefulness of intraoperative real-time direct electrical cortical and subcortical stimulations performed repetitively at every moment and each site of resection, to identify and to preserve eloquent cortical sites and subcortical pathways essential for sensorimotor and/or language functions. Indeed, in the six patients who maintained definitive neurological worsening, three deficits were due to a deep stroke (lenticulostriate arteries damaged during frontotemporoinsolunar low-grade glioma resection) and three others were caused by a glioma invasion of the entire central region, which had induced a preoperative paresis that was likely explained by a limit of the plasticity mechanisms often involved to compensate for gliomas in eloquent areas. In other words, no postoperative sequela was due to the interruption of the white fibers. Thus, this method should not be considered as an alternative to the mapping techniques mentioned earlier, but rather as a complementary method offering functional data that cannot be provided using the other techniques.

Complement to Preoperative Neurofunctional Imaging

In addition to the fact that the sensitivity of these cortical mapping methods is still not optimal despite constant efforts for its improvement (sensitivity ranging from 82–100% for the identification of sensorimotor sites and from 77–100% for the identification of the language areas), the actual mapping of white fibers remains impossible for technical reasons. This point was emphasized in the work of Hirsch, et al. “fMRI has little sensitivity for subcortical areas and, particularly, for white matter tracts. It is for this reason that functional imaging is a useful guide in preoperative and intraoperative planning, but does not replace the need for careful intraoperative mapping in regions of cerebral eloquence.” Data from our present study demonstrate further proof of this point of view, and we assert that the use of intraoperative cortical and subcortical stimulations (complementing preoperative neurofunctional mapping) represents a valuable adjunct to avoid the occurrence of a definitive postoperative deficit. Nonetheless, there are other recent developments in MR imaging that can help delineate deep white matter tracts, specifically diffusion-tensor imaging. A comparison of preoperative and intraoperative real-time direct electrical cortical and subcortical stimulations might represent a method of validating tractography as the most reliable method. Thus, this method should not be considered as an alternative to the mapping techniques mentioned earlier, but rather as a complementary method offering functional data that cannot be provided using the other techniques.
Complement to Intraoperative SSEPs

For the intraoperative identification of the sensorimotor region, one can stimulate a peripheral nerve and record the indirect SSEP from the cortex.5,18,45,47,48,54,82,86,87,111,114,135 Note, however, that the value of motor cortex mapping by using direct cortical stimulations has been previously demonstrated to be higher than by indirect cortical SSEP2 (accurate localization of the central sulcus was between 91 and 94%).18,66,111,135 Moreover, phase-reversal recording demonstrates only the central sulcus itself and offers no direct information on the particular distribution of motor function on the exposed cerebral structures.2,18 Additionally, in cases of subcortical tumor removal, resection can be limited only on the basis of indirect data, that is, when SSEPs begin to be altered. But this method is unable to provide direct information about the exact location of the thalamocortical ascending pathways or the pyramidal descending fibers. Consequently, there is a permanent double risk: to detect modifications of SSEPs while the subcortical tracts are already damaged or to have a higher sensitivity of SSEPs leading to the premature interruption of glioma removal, when the resection was not yet in contact with the functional pathways. Again, the use of repetitive subcortical electrical stimulations may allow one to solve this problem by the direct identification of sensorimotor fibers when they are encountered.

Complements to Intraoperative Direct Cortical Stimulations

Motor Evoked Potentials in Patients in a State of General Anesthesia. Although this method was improved with modified electrical parameters,130 repetitive intraoperative stimulations of the motor cortex rather than a single stimulation,46 and its combined use with SSEPs,18,69,72,140 several problems persist. First, when recording compound muscle action potentials, only the monitored muscles can be controlled; that is, there is an inability to detect and possibly to avoid motor deficits in unmonitored muscles. For this reason, Cedzich, et al.,18 asserted that monitoring of “all muscle groups at risk” seemed necessary. In the case of extensive low-grade gliomas involving subcortical regions where the pyramidal tracts converge, however, we showed that all parts of the contralateral hemibody may produce motor responses, making it difficult to predict or define all muscle groups at risk before resection. Second, as with SSEPs, motor evoked potentials give only indirect information about the location of pyramidal pathways, even with the use of repetitive stimulations, and do not allow for the direct identification of motor tracts when the resection interferes. In the same way, although authors of a recent study showed that a reduction in amplitude greater than 80% and a prolonged latency of more than 15% can be interpreted as intraoperative warning signs of potential mechanical damage to the motor system and lead to the end of resection, they emphasized that the occurrence of a complete or nearly complete and sudden nonartifactual reduction in amplitude could be attributed to a lesion of the subcortical pyramidal fibers, and that such irreversible changes in potential cannot serve as a warning sign in such cases, because they occur only after damage.88 These limitations of the evoked potential techniques may explain why 20% of sequelae, mainly due to resection of subcortical lesions in the immediate vicinity of the pyramidal tract, have been reported by Cedzich, et al.,18 who concluded that “an additional method is necessary in patients requiring localization deep in the white matter and when tumors involving motor pathways are to be removed.” We argue that the use of repetitive intraoperative subcortical stimulations could offer the complementary functional data not provided by evoked potentials, which does not exclude the simultaneous use of a multichannel electromyographic recording, as previously suggested by Yingling, et al.138

Direct Cortical Sensorimotor and Language Mappings in Patients After Induction of General or Local Anesthesia. Although authors of a large number of series reported on the use of direct electrical cortical stimulation in patients after induction of general or local anesthesia during surgery for tumors in eloquent brain areas,15,25,35,37,38,41,46,55,58,60,68,69,71,72,79,80,84,85,89,94,102,111,121,124,125,127,131,140 very few mentioned an interest in also performing intraoperative repetitive subcortical stimulations,39,133 except Berger and colleagues.5,7,9–11,51,52,81,126,138 Consequently, prolonged and even permanent postoperative neurological worsenings were reported due to the lack of accurate and repetitive white matter mapping. In a recent study in which the resection of a low-grade glioma involved the supplementary motor area, Peraud, et al.,102 reported that some patients displayed severe paresis with slow recovery because of a lesion probably occurring “in the depth of the white matter, when the most posterolateral part of the tumor [wa]s removed.” In the comments to this paper, Piepmeier confirmed that the “interruption of the descending motor fibers is a common cause of unanticipated permanent motor deficits.” Thus, Peraud, et al., concluded that because of this risk of damage to the pyramidal tract at the level of its deep inflection, “surgery for Grade II gliomas in the superior frontal gyrus is more likely to result in permanent morbidity when the resection is performed at a distance of less than 0.5 cm from the precentral gyrus or positive stimulation points.” In recent publications summarizing their entire experience,25,94 the team of Danks and colleagues, who accumulated a large series of patients with low-grade gliomas,13,26,93 described their policy of resection as being limited to within 0.5 cm of the primary sensorimotor cortex (Roux, et al.,113 had a limit of 1 cm). Note that Danks, et al.,25 mentioned that they did not use stimulation mapping of subcortical white matter in their series and according to Nikas, et al.,114 “subcortical white matter stimulation mapping is occasionally performed.” Thus, even if a complete resection rate of 57% was achieved (including pilocytic astrocytoma, ganglioglioma, and ependymoma, that is, well-demarcated tumors, with only 28% of a real World Health Organization Grade II low-grade gliomas), this rate could be optimized if no margin was left around the eloquent areas, because many low-grade gliomas come into the contact and even invade the primary sensorimotor sites.

On the basis of our experience, we were prone to stop resection immediately on contact with functional cortico-subcortical structures, a policy that automatically allowed us to improve the quality of low-grade glioma removal; that is, 30% of all resections demonstrated no signal abnormality on repeated MR images, 27% resulted in less than 5 cm³ of residual tumor, and 23% resulted in a tumor residue between 5 and 10 cm³ (totaling 80% of so-called complete [30%] and near-complete [50%] resections). This strategy seemed possible with a good reliability only because we...
systematically used the repeated subcortical stimulations during the resection to follow the white fibers closely, from the surface to the depth.31,33–36,43 This procedure allowed us to anticipate a permanent deficit, except in six patients for reasons previously explained (lenticulostriate arteries damaged in three cases and diffuse glioma infiltration of the entire central region in the other three cases), but never due to a surgical interruption of the subcortical pathways. Nevertheless, for reliability, this method necessitates repeatedly repeated subcortical stimulations. Indeed, in a recent series of patients with insular gliomas, Lang, et al.,73 used direct subcortical stimulation, but asserted that this technique “often does not provide adequate warning of ensuing neurological function, but merely reports the loss of neurological function. For example, interruption of motor fibers could occur between direct brain stimulation trials.” In their methodology, however, these authors stated that “subcortical stimulation was used infrequently during tumor resection.” This can perfectly explain why a surgical injury to the pyramidal tract may occur between two stimulation trials. Thus, online stimulations should be performed during the entire glioma removal procedure.

Finally, although authors of many studies have raised the issue of preserving (sensori)motor fibers, very few have studied the language pathways except Berger and colleagues.6,7,11,51,52,81,126 Indeed, most researchers perform electrical cortical mapping in patients harboring a tumor within language areas and the patients remain awake during resection.35,124 In these cases, however, the patient performs functional tasks without the benefit of subcortical mapping.24,25,37,85,93,102,131,132 We think that the use of subcortical stimulation represents a valuable adjunct in patients in whom local anesthesia has been induced. Indeed, the main problem of this procedure is its duration, followed by the fatigue of the patient. Consequently, in the last stages of resection, patients often demonstrate a slowness in their language. At this time, it is not easy to differentiate language disturbances due to fatigue or the fact that the resection has interfered with language pathways. Thus, the surgeon must distinguish between two risks: either to stop the resection prematurely while speech disturbances are due to patient fatigue (and risk leaving residual tumor that could have been removed without inducing permanent aphasia), or to continue glioma removal while speech disorders represent a warning of injury to the language pathways (and risk causing a major language deficit during the ensuing resection). To solve this problem, we advise the use of direct subcortical stimulation in a patient who successfully performs functional tasks after several minutes of rest. If the stimulation does not disrupt language, the surgeon will know that it is possible to complete the tumor resection without additional risk of sequelae. Conversely, if stimulation elicits the slightest speech disturbance, an immediate interruption of the resection is clearly mandatory.

Our experience is in accordance with those of the few researchers who have relied on the systematic use of the intraoperative subcortical stimulations in association with cortical mapping. Indeed, Vinas, et al.,133 reported that “during resection of the structural lesions, intraoperative stimulation was continued in the subcortical pathways, and five patients had positive responses on areas not identified by the functional PET.” They then concluded that “intraoperative mapping still remains the main means to avoid neurological damage as it can be performed during the entire surgical procedure to avoid damage to cortex and pathways.” This was a small series, however, including only 12 patients. More recently, Eisner, et al.,39 also showed that “electrophysiologically controlled surgery by bipolar electric stimulation of the cerebral cortex and descending fiber system is a very effective instrument for detecting cerebral functions in exact spatial distribution.” Again, this was a heterogeneous and small series. It was the team of Berger and colleagues.6,7,9,10,11,51,81,128,138 who honed the regular use of intraoperative cortical and subcortical electrical mapping in glioma surgery. Our experience with a homogeneous consecutive series of 103 patients with low-grade gliomas seems clearly to confirm the value of such a procedure. Although Berger and colleagues reported that a margin of 7 to 10 mm around the language areas resulted in significantly fewer permanent postoperative linguistic deficits, we noted no higher rate of definitive language worsening despite a resection coming in contact of the language sites (but a higher rate of transient postoperative aphasia). This discrepancy may be partly explained in the work of Haglund, et al.,52 regarding the sphere of influence of electrocortical stimulation—all gliomas in their patients were located in the temporal lobe, whereas many low-grade gliomas in patients in our study invaded the frontal lobe. Indeed, results of a recent fMR imaging/electrostimulation correlation study105 demonstrated that in the temporal lobe, an electrostimulation radius of 10 mm must be assumed to achieve a nearly 100% sensitivity in fMR imaging, whereas in the frontal lobe, a smaller stimulation radius of 5 mm can be used to achieve 100% sensitivity. These findings are consistent with reports that essential language sites are more concentrated in the frontal rather than in the temporal lobe.98,99

Limitation of Intraoperative Subcortical Electrical Mapping

Despite the contribution of subcortical stimulation, two kinds of limitation persist: functional and oncological. 1) Functional limitation: all resections in our patients were stopped when functional fibers detected on stimulation were encountered. No postoperative sequela was due to the interruption of the white fibers. Despite systematically verifying the integrity of functional networks at the end of the glioma removal, however, neurological functioning in 80% of patients worsened in the immediate postoperative stage. This could be explained by the fact that secondary eloquent corticosubcortical areas—namely those participating in, but not essential to, function—were surgically removed (such as the supplementary motor area or the insula, known to induce a possible transient dysfunction with secondary recovery when resected).31,36,43,76,79,85,140 Given that the surgical methodology was the same in all 103 patients, our data indicate that the subcortical stimulations allow one to identify and then to preserve the pathways essential to a function, but cannot be used to predict the occurrence or the intensity of a transitory postoperative deficit.

2) Oncological limitation: despite additional published arguments favoring the positive impact of the quality of resection on the natural history of a low-grade glioma,8,9,11,63,65,91,93,101,103,104,117 there is currently no absolute certainty regarding the long-term efficacy of such a therapeutic strategy. Consequently, although subcortical mapping may allow for
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greater tumor resection while sparing deep white matter tracts and therefore eloquent function, we have yet to prove an impact on long-term survival. Thus, further series in which researchers study oncological results of low-grade glioma surgery with a long follow up are mandatory to determine whether a less aggressive resection with minimization of the transient immediate postoperative deficit would be better for the patient.

Conclusions

The 94% rate of favorable functional results in this series supports the systematic use of cortical and repetitive subcortical electrical stimulations as an adjunct to other methods of functional mapping during resection of low-grade gliomas in eloquent areas. Such a strategy allows the neurosurgeon to perform a tumor resection according to functional boundaries and then to optimize the benefit (quality of glioma removal)/risk (postoperative definitive deficit) ratio. The drawback of this procedure is the frequent occurrence of immediate postoperative neurological worsening—80% in our series, which was in accordance with recent data from the Mayo Clinic experience of 74% deficits. Although these deficits are secondarily regressive, they often necessitate rehabilitation therapy for 1 to 3 months, and another 3 to 6 months to return to a normal socioprofessional life. Consequently, it is mandatory to give clear information to the patient and his or her family preoperatively, which can be most specific by using preoperative neurofunctional imaging. Also note that beyond functional recovery, a patient’s delayed postoperative status may be improved in comparison with his or her preoperative status (10% of patients in our series) and epilepsy better controlled in 80% of cases.

Moreover, the use of intraoperative real-time direct subcortical stimulation can lead to a better understanding of the brain functional connectivity—especially complex and poorly studied with regard to language—and thus likely allow for future improvements in surgical preplanning. Data from both cortical and subcortical functional mappings should be used and perhaps partly provided by DW MR imaging tractography if this method can be validated using subcortical stimulations.

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