Multimodal Surgical Management of Cerebral Lesions in Motor-Eloquent Areas Combining Intraoperative 3D Ultrasound with Neurophysiological Mapping

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Abstract

Background Resection of tumors adjacent to motor pathways carries risks of both postoperative motor deficit and incomplete resection. Our aim was to assess usefulness and limitations of a multimodal strategy that combines intraoperative ultrasound (iUS) guided resection with intraoperative neurophysiology.

Methodology This is a prospective study of 25 patients with brain lesions adjacent to motor areas who underwent intracranial surgery with assistance of the iUS guidance system and intraoperative neurophysiological monitoring and mapping. Pathologies treated included 19 gliomas, 3 metastases, 1 anaplastic meningioma, 1 arteriovenous malformation (AVM), and 1 ependymoma. The iUS-guided lesion removal accuracy and the extent of resection were estimated and compared with a 30-day postoperative brain MRI. The results were assessed considering the extent of resection related to 6-month motor function outcome.

Results iUS was accurate in checking the extent of resection in 17 patients, whereas in 8 cases the decline of the iUS images quality did not allow a valuable assessment. Positive mapping was obtained in 16 patients. Gross total resection was achieved in 16 patients. In five of nine cases with subtotal resection, surgery was stopped because a functional area was reached. In four patients, tumor removal was limited due to the difficulty of identifying neoplastic tissue. Motor function worsening was transient in six patients and permanent in two.

Conclusions The integrated use of intraoperative neuromonitoring to identify motor areas and iUS to identify tumor–tissue interface could help increase the rate of radical resection respecting the eloquent areas.

Keywords
- intraoperative 3D ultrasound
- US-guided brain surgery
- cortical stimulation
- brain mapping
- brain tumors

Introduction

Surgery of lesions in eloquent brain areas is challenging because the potential benefits obtained by a radical resection must be balanced against the risks of neurological morbidity and low quality of life. The intraoperative neurophysiological monitoring (IONM) can identify with high reliability cortical and subcortical eloquent areas and therefore reduce the risks of disabling neurological deficits.[1–10]

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Radical resection depends on the ability to distinguish the neoplastic from the healthy tissue. It is not uncommon, particularly in intra-axial tumors, that healthy brain and tumor tissue have a blurred interface, making a gross total resection (GTR) difficult. For this reason, some intraoperative diagnostic tools like intraoperative ultrasound (iUS), intraoperative computerized tomography (CT), intraoperative magnetic resonance imaging (MRI), 5-aminolevulinic acid (5-ALA) have been developed to help in identifying tumor remnants not visible to the "naked eye" and then optimizing the resection. IONM and intraoperative imaging (as well as 5-ALA) can identify the functional as well as anatomical limits of the tumor resection. Therefore, their integration could be helpful in obtaining the so-called maximal safe resection.

The aim of the present study was to assess the utility and limitations of a multimodal approach to cerebral lesions in motor-eloquent areas in which iUS-guided resection had been combined with intraoperative neurophysiology (somatosensory evoked potential [SSEP] and motor evoked potential [MEP] monitoring and cortical and subcortical mapping).

Materials and Methods

This is a prospective study conducted at the Department of Neurosurgery of the University Hospital of Sassari between March 2015 and April 2018. All the enrolled patients provided their written consent for anonymous data collection and inclusion in the study.

Inclusion Criteria

- The inclusion criteria for the study were the following: Brain lesions located within or in proximity to the motor cortex or motor pathways (central sulcus, insula, thalamus, and brainstem); I indication for total resection, GTR, or subtotal resection (STR).

Exclusion Criteria

- The exclusion criteria for the study were the following: Severe preoperative motor deficit (modified Medical Research Council [mMRC] scale 0/5 to 2/5); indication for biopsy only; extra-axial lesion (meningioma); general contraindications to surgery (severe cardiac or pulmonary dysfunction).

Twenty-five patients (16 males and 9 females) were included (see ►**Table 1**). The average age was 51.2 years (range 17–74 years). Clinical onset was as follows: seizures in 8 patients, mild to moderate motor deficit in 9 patients, headache in 2 patients, cognitive impairment in 2 patients, behavior disorders in 2 patients, and cerebral hemorrhage in 2 patients.

Lesion Localization

- Fifteen lesions in the posterior frontal lobe, 4 lesions in the parietal lobe, 2 fronto-insular lesions, one 1 temporo-insular lesion, 1 thalamic lesion, 2 lesions in the fourth ventricle floor.

The motor function was assessed according to the mMRC system; the preoperative motor function was as follows: Fifteen patients (60%) had normal muscle strength (mMRC 5/5), 5 patients (20%) a mild motor deficit (mMRC 4/5), and 5 patients (20%) a moderate motor deficit (mMRC 3/5). All the patients underwent preoperative imaging with head CT scan with contrast enhancement (CECT) and brain MRI with gadolinium; in two patients, a tractographic study was also performed.

All surgical procedures were performed by two neurosurgeons (D.P. and R.B.), both well trained in brain surgery and intraoperative 3D iUS and IONM. All the patients received antiepileptic therapy with levetiracetam and phenytoin according to the following protocol: levetiracetam 1,000 mg in two administrations per day to a maximum of 3,000 mg per day in two administrations (until complete control of seizures) starting 5 days before operation and lasting for at least 1 week after (suspended in patients without a pre- and postoperative history of seizures); phenytoin 250 mg as loading dose at the induction of general anesthesia, then 100 mg every 8 hours for 7 days, and then gradual withdrawal. All interventions were performed with neuronavigation, and intraoperative navigated US (SonoWand system Sonowand Invite TM, Trondheim, Norway) and intraoperative neurophysiology with the NIM Eclipse Medtronic system (NIM Eclipse Medtronic, Minneapolis , MN, USA).

Anesthesia

All patients underwent surgery under total intravenous anesthesia (TIVA); it was induced with bolus of propofol and remifentanil and further maintained with propofol and remifentanil. The intermediate-acting muscle relaxant rocuronium was administered for intubation purposes only. Recovery from muscle relaxation was tested by using the "train-of-four" (TOF) technique (percutaneous stimulation of the right median nerve [40 mA, 0.2-ms pulse duration] and recording of the compound motor action potentials [MAP] from the right abductor pollicis brevis muscle). TOF peripheral nerve stimulation producing MAP $\geq$90% was required before motor cortex stimulation (mapping) was started.

Neuronavigation and Intraoperative Ultrasound

The neuronavigation system in use since 2014 in our department (SonoWand) is a single rack system that can be used as either a stand-alone neuronavigation system using preoperative images (CT or MRI) or as a stand-alone US machine providing real-time intraoperative 2D images as well as a navigable 3D images (which allows navigation based solely on the iUS with no need of preoperative images). The system is also equipped with a combined mode that uses both preoperative images and iUS (either 2D or 3D). In this modality, the system automatically superimposes the actual iUS images on the corresponding preoperative CT/MRI slice, thus allowing anatomical orientation and comparison of US details with the corresponding CT or MRI. The system has been previously described elsewhere.[11,12]

Table 1 Patients population

Patient no.	Sex	Age (y)	Lesion localization	Diagnosis	Pre-op motor evaluation	mMRC	Resection grade	US visibility
1	M	17	Posterior frontal	Diffuse astrocytoma	Normal	5	GTR	Mair 1
2	M	72	Parietal	Anaplastic astrocytoma	Mild paresis (leg)	3	STR	Mair 3
3	M	37	Fourth ventricle floor	Pilocytic astrocytoma	Normal	5	STR	Mair 2
4	M	51	Posterior frontal	Glioblastoma	Slight paresis (face–arm)	4	GTR	Mair 2
5	F	52	Fronto-insular	Diffuse astrocytoma	Slight paresis (face)	4	GTR	Mair 2
6	M	74	Posterior frontal	Glioblastoma	Mild paresis (leg)	3	GTR	Mair 2
7	M	69	Fronto-insular	Glioblastoma	Mild hemiparesis (face–arm–leg)	3	GTR	Mair 2
8	F	65	Posterior frontal	Diffuse astrocytoma	Normal	5	STR	Mair 2
9	M	60	Posterior frontal	Metastasis (lung)	Mild paresis (arm–leg)	3	STR	Mair 3
10	M	40	Posterior frontal	Anaplastic astrocytoma	Normal	5	GTR	Mair 1
11	F	39	Posterior frontal	Anaplastic meningioma (WHO III)	Slight paresis (arm–leg)	4	GTR	Mair 3
12	F	53	Posterior frontal	Glioblastoma	Normal	5	GTR	Mair 2
13	M	25	Thalamic	Glioblastoma	Normal	5	STR	Mair 3
14	M	68	Posterior frontal	Glioblastoma	Normal	5	STR	Mair 3
15	M	20	Posterior frontal	Anaplastic astrocytoma	Normal	5	STR	Mair 2
16	F	65	Posterior frontal	Glioblastoma	Normal	5	GTR	Mair 3
17	M	51	Posterior frontal	Arteriovenous malformation	Normal	5	GTR	Mair 3
18	M	39	Posterior frontal	Diffuse astrocytoma	Normal	5	GTR	Mair 2
19	F	34	Fourth ventricle floor	Ependymoma	Normal	5	GTR	Mair 3
20	F	44	Parietal	Metastasis (lung)	Normal	5	GTR	Mair 3
21	M	72	Posterior frontal	Glioblastoma	Normal	5	STR	Mair 2
22	M	53	Parietal	Glioblastoma	Normal	5	STR	Mair 2
23	M	53	Posterior frontal	Glioblastoma	Mild paresis (face–arm)	3	GTR	Mair 3
24	F	66	Parietal	Metastasis (lung)	Slight paresis (leg)	4	GTR	Mair 3
25	F	61	Temporo-insular	Glioblastoma	Slight hemiparesis (face–arm–leg)	4	GTR	Mair 3

Abbreviations: GTR, gross total resection; STR, subtotal resection.

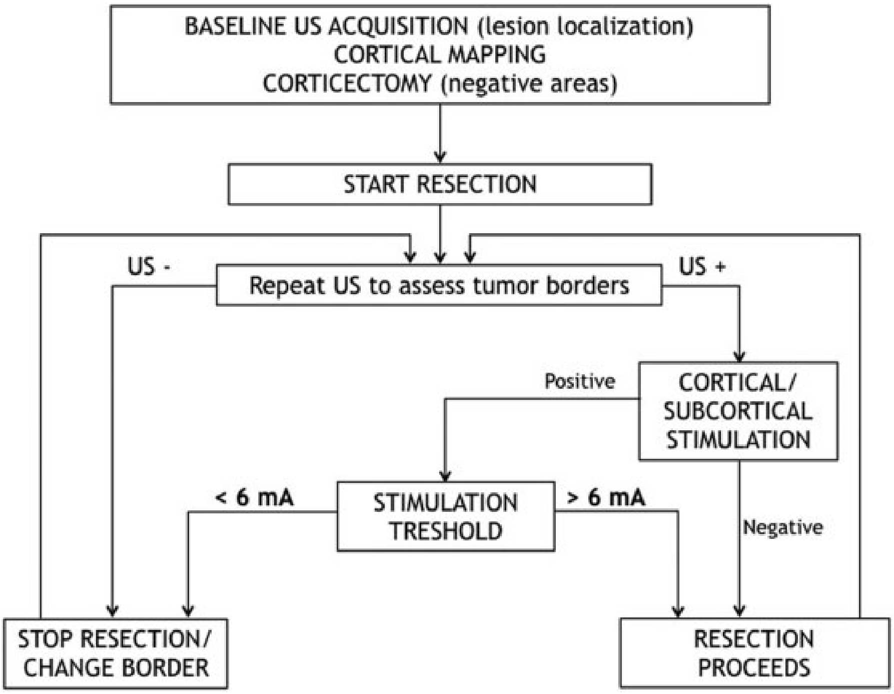

Fig. 1 Algorithm describing surgical protocol.

In all the patients, in addition to the previously described complete neuroradiological diagnostic protocol, a preoperative volumetric examination with standard skin-adhering fiducials placed on the scalp was acquired on the day prior to surgery (MRI with gadolinium in 19 patients and CECT in 6 patients). Images were transferred to the neuronavigation system. The system is used at the beginning of the procedure to plan the surgical approach (position, skin flap, and craniotomy). After the craniotomy, it is possible to acquire US scans in a few seconds (either 2D or 3D navigable) whenever it is necessary to update the information as brain shift occurs and neuronavigation accuracy is thereby lost. US visibility of different pathologies was assessed using the classification proposed by Mair et al in 2013,[13]. Grade 0 describes lesions that are not visible. Grade 1 describes tumors difficult to visualize without an exact border with the normal brain tissue. Grade 2 is a clearly identifiable lesion lacking a clear border with the normal brain tissue and grade 3 is a lesion clearly identifiable with a clear border with the normal tissue. Initial visibility assessment was performed at the time of surgery by the operating neurosurgeon. All iUS images were stored and independently reviewed postoperatively by the other experienced surgeon. Both evaluations were matched, and the final lesion's visibility grade was established.

Neurophysiology

Corkscrew electrodes were placed subcutaneously at C3, C1, Cz, C2, and C4 according to the international 10–20 electroencelphalography (EEG) system (the exact position of the scalp electrodes in some cases has been modified according to the surgical flap) for EEG and SSEP recording and for transcranial electrical motor cortex stimulation (TES). MEPs were recorded by using subdermal needle electrodes for the abductor pollicis brevis and tibialis anterior muscles bilaterally, and for the biceps brachii and extensor digitorum communis muscles contralateral to the affected hemisphere. However, depending on the tumor location, additional muscles were monitored, for example, quadriceps femoris muscles for parafalcine tumors or orbicularis oris muscle for frontal operculum tumors. TES MEPs were monitored in an alternating fashion with SSEPs. DCS ("mapping") was performed by using a handheld monopolar probe with a modified multipulse stimulation technique: frequency of 300 Hz; monophasic current, trains of 8 pulses (train frequency of 3 Hz), and maximum stimulation intensity of 18 mA.[14,15]

Continuous EEG recording was used to identify epileptic electrical activity. In the event of intraoperative epileptic seizures and/or pre-epileptic EEG alterations, the surgical field was immediately irrigated with cold saline.

Surgical Intervention

Patient positioning was optimized to ensure that the operative cavity could be filled completely with saline to improve US image quality. The baseline MEP and SSEP were acquired before starting the resection, to have not only a comparison throughout the whole surgical procedure but also the confirmation of a complete decurarization according to the TOF data. Surgical flaps and craniotomies were planned with navigation to expose completely the lesion and a margin of surrounding healthy brain tissue. A baseline iUS scan was acquired after elevating the bone flap and before opening the dura (when brain shift is virtually absent compared with preoperative images), then the 3D US images were integrated into the navigation database to localize the lesion, define its margins, dimensions, morphology, and echogenic features, and to assess initial visibility grade. The cortical mapping

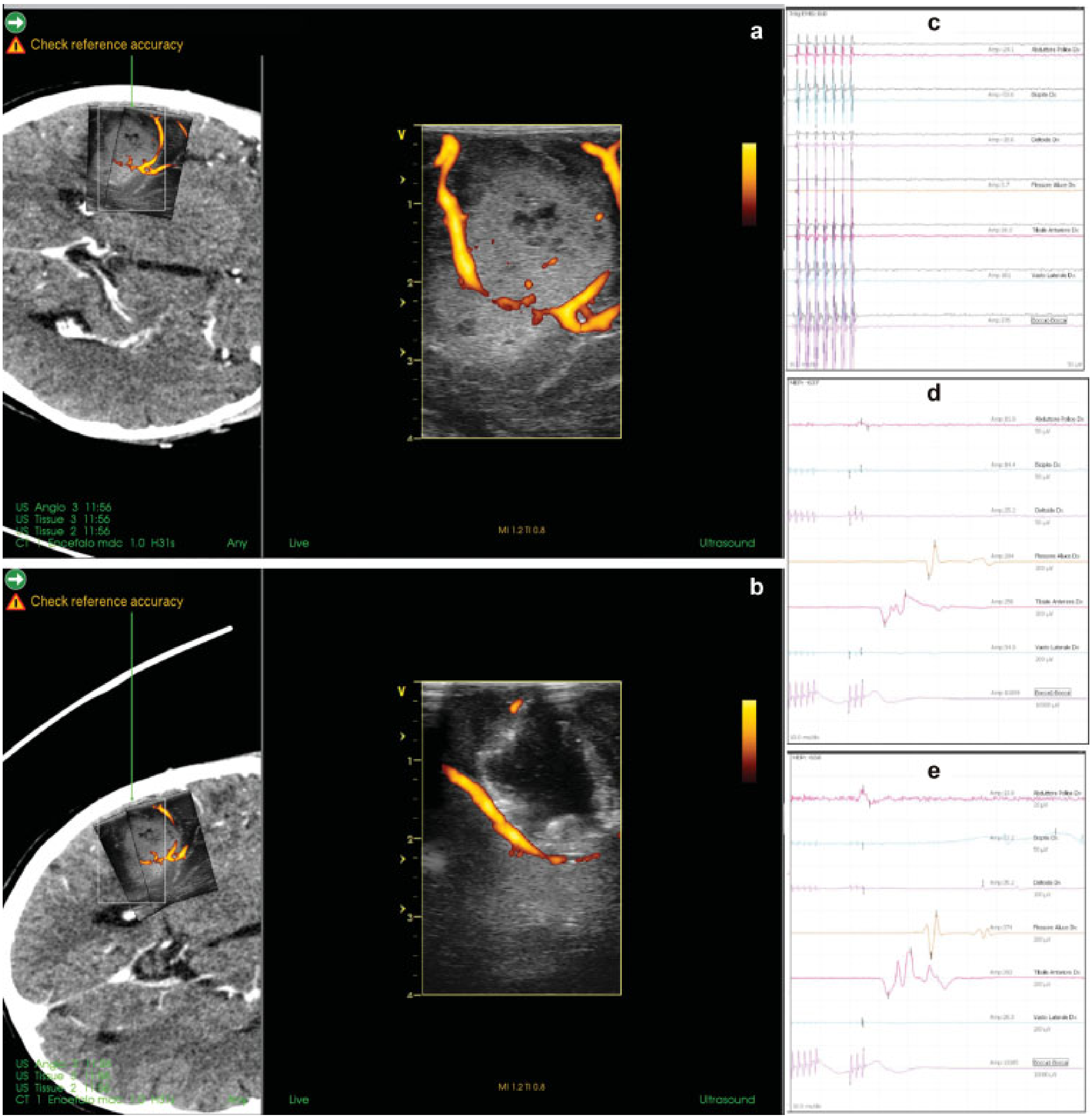

Fig. 2 Patient no. 20. (a) Baseline intraoperative ultrasound (iUS acquisition) showing tumor and adjacent vessels, negative cortical mapping, start resection following tumor borders. (b) Final US scan showing complete tumor resection. (c) Negative subcortical mapping (15 mA). (d) Baseline motor evoked potential (MEP) recording. (e) MEP recording at the end of the procedure that appears unchanged with respect to baseline.

started with an intensity of stimulation of 6 mA up to a maximum of 18 mA. The approach to the tumor was based on both iUS and functional data to perform the corticotomy on areas with negative mapping ("shortest and safest" trajectory). During resection, US acquisitions and stimulations to check the anatomical and functional margins were used alternatingly (see the algorithm in ►**Fig. 1**). Subcortical stimulations was performed with an initial intensity of 15 mA, which corresponds to a distance of ~15 mm from the corticospinal tract (CST).[16–18] In case of a positive response, the intensity was reduced in steps of 2 mA until identifying a threshold of 6 mA which, was arbitrarily chosen as a safe distance to the CST (~6 mm), in our opinion useful to complete resection and hemostasis with low risk. In case of positive response to subcortical stimulation with a threshold less than 6 mA or in case of negative US, the resection was stopped; moreover, surgery also was stopped if MEP amplitudes (acquired from TES) permanently decreased to >50% compared with the baseline.

Surgical Algorithm

- NEGATIVE mapping: using repetitive US, negative stimulation and uneventful MEP and SSEP monitoring, the resection was continued until complete resection (►**Fig. 2**).
- POSITIVE mapping over 6 mA: using repetitive US, the resection was continued until the stimulation was

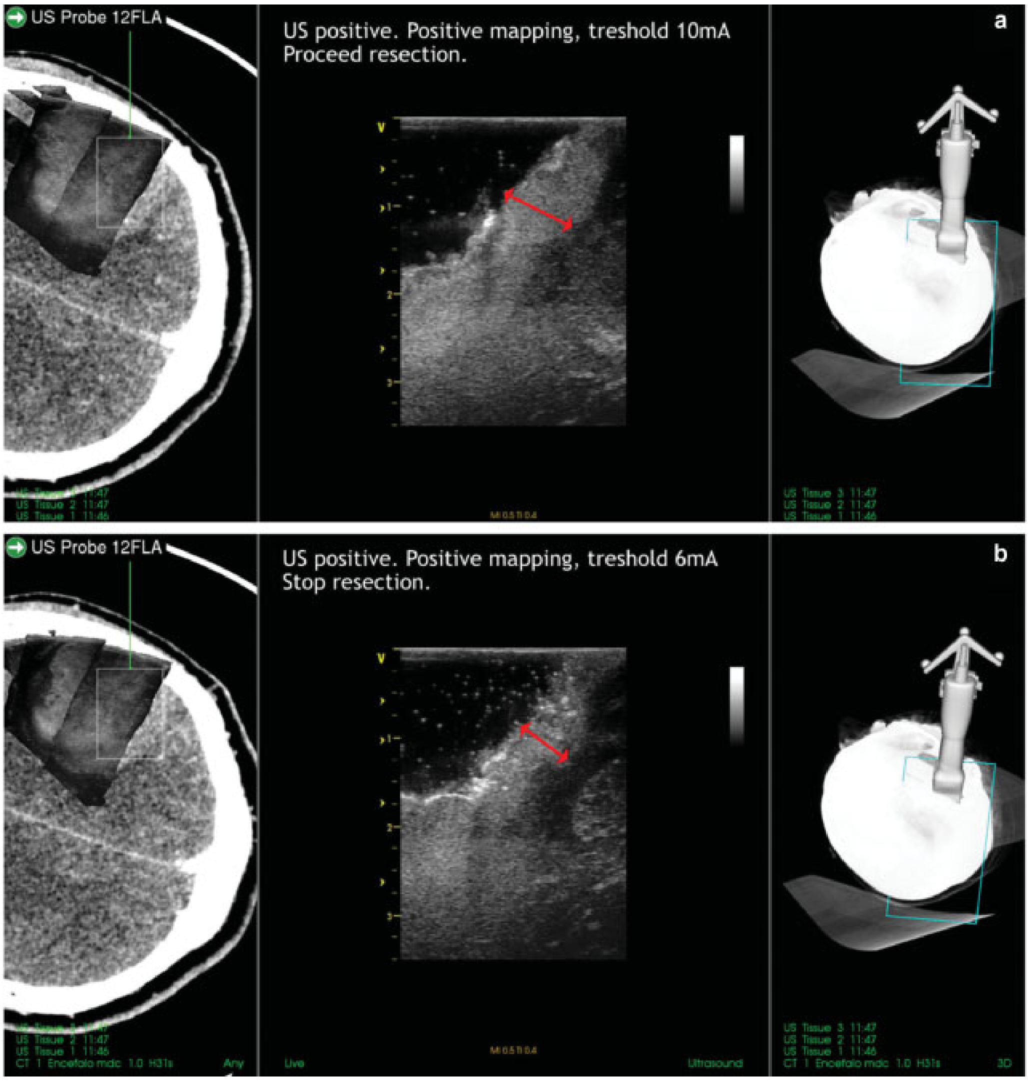

Fig. 3 Patient no. 2. (a) Intermediate intraoperative ultrasound (iUS) acquisition showing residual tumor in vicinity to the motor pathways; positive mapping, with threshold of 12 mA. Resection proceeds until mapping threshold dropped to <8 mA. (b) Final iUS showing residual tumor (subtotal resection).

positive at 6 mA and higher or complete resection was achieved (►**Fig. 3a**).

- POSITIVE mapping: the resection was stopped if the stimulation was positive at less than 6 mA (►**Fig. 3b**).

If surgical artifacts and/or low US visibility of the tumor prevent US control of the resection, the operation was continued based on neurophysiological data and microscopic view. At the end of the procedure, final stimulations were performed and MEP and SSEP are recorded as well to confirm the functional integrity of the CST (►**Fig. 2**). All the patients underwent immediate postoperative head CT scan to rule out surgical complications.

Clinical and Radiological Follow-up for at Least 6 Months

The motor function was evaluated by a physiatrist together with a neurosurgery resident (D.G.), conforming to mMRC scale (1–5) and according to the following timetable: preoperatively 12 hours after admission to intensive care unit and then at the first and second week and the first, third, and sixth month after surgery. In case of hemiparesis with different scoring for the face, arm, and limb, the worst value was chosen as the final score.

Extent of resection (EOR) was assessed by using a 30-day postoperative brain MRI with gadolinium (which was evaluated by the neuroradiologist); GTR was defined as a resection of more than 98% of the tumor volume based on volumetric measurements. Subsequent radiological follow-up and therapeutic protocol were based on histology findings according to the literature.

Results

Pathologic Findings

- Fourteen high-grade gliomas (56%): 11 glioblastomas (GBMs; WHO grade IV) and 3 anaplastic astrocytomas (WHO grade III); 5 low-grade gliomas (LGGs; 20%): four diffuse astrocytomas (WHO grade II) and one pilocytic astrocytoma (WHO grade I); 3 metastases from lung carcinoma (12%); 1 anaplastic meningioma (WHO grade III; 4%); 1 arteriovenous malformation (4%); 1 ependymoma (WHO grade II; 4%).

Intraoperative Data: Ultrasound

US visibility of lesions according to the Mair grading system at the beginning of the procedure (►**Table 1**): Two lesions (8%; Mair 1). 11 lesions (44%; Mair 2) and 12 lesions (48%; Mair 3).

iUS was accurate in checking the EOR in 17 patients (68%): in the remaining 8 (32%) lesions (4 GBM, 2 anaplastic astrocytomas, 2 diffuse astrocytomas), the deterioration of the iUS images quality, due to the low visibility of the lesion and/or surgical artifacts (presence of cottons, hemostatic material, microhemorrhages, reinforcement artifacts, etc.), did not allow a valuable assessment. Of the 17 patients in whom iUS resection control was found to be persuasive, 10 had lesions graded as Mair 3, whereas the other 7 had Mair 2. The 8 patients with iUS-guided resection control considered inadequate showed the following Mair grading: two Mair 3 cases, four Mair 2 cases; and two Mair 1 cases.

Intraoperative Data: Neurophysiology

Positive intraoperative mapping was obtained in 16 patients (64%; see ►**Table 2**): The primary motor area (PMA) was identified in four patients and the CST was identified in three patients. Both PMA and CST were identified in nine patients. Despite high-intensity stimulation (up to 18 mA), no eloquent motor area (neither cortical nor subcortical) was detected in nine cases. All the patients showed, at the time of stimulation, pre-epileptic EEG alterations that were promptly resolved by the irrigation of the exposed brain tissue with cold saline. Six patients had intraoperative seizures that also ceased after irrigation with cold saline solution and 4-ml propofol bolus.

Extent of Resection

The assessment of the EOR was based on brain MRI with gadolinium performed 30 days after surgery (see ►**Table 2**). GTR was obtained in 16 patients, whereas STR was obtained in the remaining 9 patients. In five of the nine cases with STR, resection was stopped considering the intraoperative neurophysiological data, whereas in the other four, it was due to the difficulty of clearly identifying residual neoplastic tissue; three of these four patients showed residual tumor on 30-day post-operative MRI which was not in vicinity to the motor pathway. Of the five patients in whom resection was interrupted considering the intraoperative neurophysiological data, three patients had a positive mapping and tumor remnant in iUS (see ►**Fig. 3**). In the other two patients, subcortical stimulation with <6 mA was positive, but iUS was considered unreliable (30-day MRI confirmed residual tumor as well).

In the eight cases with iUS considered unreliable, we achieved two GTRs and six STRs (including two of the five patients in whom resection was bot continued because of the neurophysiological mapping data). In all 17 patients in whom the image quality was considered persuasive, EOR, assessed by the final iUS, was confirmed by the 30-day MRI (3 STRs and 14 GTRs).

Clinical Outcome

Complications: one patient presented a postoperative epidural hematoma and another one a chronic subdural hematoma 10 days after surgery. Both were surgically treated without sequelae. Two patients died within 6 months: the first due to severity of the disease, the second one because of cardiac pathology. The remaining 23 patients completed the 6-month follow-up. The patients were subdivided into three categories: worsened, stable, and improved compared with the preoperative status. At the first evaluation after surgery, 1 patient showed immediate improvement, 15 remained stable, and 9 (36%) deteriorated. Of the nine worsened cases, five lost 1 point on the mMRC scale, three lost 2 points, and one patient had a reduction of 3 points on the mMRC scale. The aggravated motor dysfunction was transient in seven cases and permanent in two. When comparing the final with the preoperative motor performance, we observed following results: 9 patients improved (36%), 14 remained stable (56%), and 2 got worse (8%). Particularly, at the end of the follow-up, the patients without motor deficits (mMRC 5/5) increased from 13 (before the operation) to 20 patients.

In terms of the relationship between mapping and motor outcome (see ►**Table 2**), of the 16 patients with positive mapping, 8 showed postoperative motor deterioration (transient in 6 and permanent in 2). Of the nine patients with negative intraoperative mapping, only one showed transient worsening of motor strength, whereas the other eight were stable; none of them showed motor deficits after 6 months (absence of false negative results).

The relationship between EOR and motor outcome: among patients with GTR, the first postsurgery neurological evaluation showed worsening in six patients, improvement in one patient, and nine patients remained stable. Of the nine patients with STR, three showed deterioration, whereas the other six remained stable. Of the two cases with permanent motor worsening, one underwent GTR, whereas the other underwent STR.

Comparing the preoperative with the postoperative motor performances, the motor function stabilized within 4 weeks in 24 patients (including 5 of the 6 patients with transient deterioration); only one patient with severe postoperative worsening recovered completely but very slowly after prolonged hospitalization in a rehabilitation institute.

Discussion

Tumor surgery in motor-eloquent areas represents a challenge for neurosurgeons since radical resection and neurological deficit avoidance are both of a great value. GTR gives great benefit from an oncological point of view; however, it may lose value in terms of patient's quality of life and consequently survival expectation if neurological deficits happen.

Table 2 Extent of resection, ability to check resection with US, cortical/subcortical mapping, and motor outcome

Patient no.	US visibility grade	Resection control	Resection grade	Mapping		Motor function (mMRC)						
				Motor cortex	CST	Pre–op	Post–op day 1	1 wk	2 wk	1 mo	3 mo	6 mo
1	Mair 1	No	GTR	Found	Found	5	4	4	4	5	5	5
2	Mair 3	Yes	STR	Found	Found	3	3	3	3	3	3	3
3	Mair 2	No	STR	–	Found	5	3	3	3	4	4	4
4	Mair 2	Yes	GTR	Found	Found	4	2	3	3	4	4	4
5	Mair 2	Yes	GTR	Found	Found	4	3	3	4	4	5	5
6	Mair 2	Yes	GTR	Found	Found	3	1	2	2	2	2	2
7	Mair 2	Yes	GTR	Found	Found	3	4	5	5	5	5	5
8	Mair 2	Yes	STR	Found	Found	5	4	4	4	5	5	5
9	Mair 3	Yes	STR	Found	–	3	3	4	4	4	4	4
10	Mair 1	No	GTR	Found	Found	5	5	5	5	5	5	5
11	Mair 3	Yes	GTR	Found	–	4	4	4	4	5	5	5
12	Mair 2	Yes	GTR	–	–	5	4	5	5	5	5	5
13	Mair 3	No	STR	–	–	5	5	5	5	5	5	5
14	Mair 3	No	STR	–	–	5	5	5	5	5	5	5
15	Mair 2	No	STR	Found	Found	5	4	5	5	5	5	5
16	Mair 3	Yes	GTR	–	–	5	5	5	5	5	5	5
17	Mair 3	Yes	GTR	Found	–	5	5	5	5	5	5	5
18	Mair 2	Yes	GTR	–	Found	5	2	2	2	2	3	5
19	Mair 3	Yes	GTR	–	Found	5	5	5	5	5	5	5
20	Mair 3	Yes	GTR	–	–	5	5	5	5	5	5	5
21	Mair 2	No	STR	Found	–	5	5	5	5	5	5	–
22	Mair 2	No	STR	–	–	5	5	5	5	5	5	–
23	Mair 3	Yes	GTR	–	–	3	3	4	4	5	5	5
24	Mair 3	Yes	GTR	–	–	4	4	5	5	5	5	5
25	Mair 3	Yes	GTR	–	–	4	4	5	5	5	5	5

Abbreviations: CST, corticospinal tract; GTR, gross total resection; mMRC, modified Medical Research Council; STR, subtotal resection; US, ultrasound.
Note: – denotes looked for but not found.

To evaluate the possibility of obtaining a maximal tumor resection with low morbidity (concept of maximal safe resection), we studied 25 patients affected with brain lesions adjacent to motor-eloquent areas or pathways who underwent surgery with the assistance of intraoperative navigated US and IONM.

Since we did not want to make assessments on the oncological outcome (ours was a small and heterogeneous case series) but just evaluate the motor function performance related to EOR, we decided to limit the follow-up period to only 6 months.

The need to limit neurological morbidity without excessively reducing the EOR has led, over the years, to the development of intraoperative neurophysiological techniques to continuously assess neurologic performance during the surgical procedure (monitoring) and localize critical cortical and subcortical areas (mapping).[1–3,5–10,19,20] IONM is used to assist surgery for lesions adjacent to different eloquent areas (motor, language, visual, memory, and so on).[1,4,9] Pathologies located in motor areas, probably due to the strong impact of a motor deficit on patient's daily life, are among the most studied. There are several case series dealing with monitoring and mapping of the motor system.[2,8,14,15,21–23] Unlike other eloquent areas, pathologies in motor areas may continuously be evaluated in terms of motor functional integrity by means of MEP monitoring (TES MEP and DCS MEP). MEP monitoring is a useful predictor of deficits; however, its value as a "warning sign" is limited and sometimes not able to prevent a CST injury[24]; therefore, it is combined with functional mapping by using direct electrical stimulations. Mapping is considered the most reliable and safest method to guide the resection of tumors in motor areas.[4,9,10,24] To optimize mapping efficacy Raabe et al[25] and Schucht et al[26] have recently proposed a continuous subcortical stimulation integrating a monopolar mapping probe at the tip of a new suction device. This method guarantees a continuous and dynamic mapping and ensures a full and constant covering of the surgical field (avoiding the alternations of resection and stimulations). Of 69 patients affected with lesions in motor-eloquent areas, treated with this method, only 2 had permanent deficits, both as a consequence of vascular injury.[25,26] The efficacy of the continuous stimulation is also confirmed by Shiban et al who used a ultrasonic surgical aspirator connected to a stimulation system to perform a continuous mapping.[23]

In our current experience, mapping was safe and reliable. Through cortical and subcortical stimulation, it was possible to identify motor areas in 16 of 25 patients (64%). The PMA was mapped in four cases, the CST in three cases, and both PMA and CST in nine cases. None of the patients with negative mapping experienced an unexpected permanent neurological deficit (absence of false negative results). Among the 16 patients with positive mapping, a postoperative deterioration of motor function was seen in 8 cases, which was permanent in 2 of them. Of the remaining six patients with transient worsening, one recovered after 2 months, whereas the other five improved and within 3 weeks. The possibility of a postoperative deficit, particularly in patients who have had positive intraoperative mapping, is also described by other authors; however, this does not reduce the reliability of the method. In a large retrospective series of 294 patients by Keles et al in 2004,[8] the authors reported the incidence of postoperative motor deficits after surgical resection of gliomas in the motor area with the aid of intraoperative mapping. In their study, the motor pathway was detected in 45% of patients. The incidence of permanent postsurgical motor deficit was 7.6% in the cases with positive cortical and subcortical mapping, but dropped to 2% in the cases with negative subcortical stimulation.

Other two large series published by Carrabba et al in 2007[2] and Seidel et al in 2013[24] reported similar data. They treated, respectively, 146 and 100 patients with tumors adjacent to motor pathways. Carrabba et al reported permanent motor deficits in 5.4% of all cases, whereas 42% experienced transient deficits. Motor deficits were more frequent in cases with positive mapping (59.3%) than in those with negative mapping (14.5%).[2] Seidel et al observed transient deficits in 30% and permanent deficits in 5% of the cases.[24] The association between postoperative motor deficits and positive mapping probably indicates that the tumor resection was close to the CST. Our study, like other existing literature data, showed that recovery in patients with transient deficits generally occurs within 3 to 4 weeks.[2,4,8,19]

A meta-analysis published in 2012[4] showed that the glioma surgery with intraoperative stimulation mapping (ISM) does not compromise the EOR, and GTR is more frequently achieved with ISM than without it. The authors concluded that ISM should be universally implemented as standard of care for glioma surgery.[4] These conclusions are supported by a review by Sanai and Berger in which the authors affirm that cortical and subcortical mapping can safely identify corridors for resection, as well as define the limits of resection.[9] Although we agree that intraoperative neurophysiology does not reduce EOR, we think that the limits of the resection could be better defined by integrating IONM with intraoperative diagnostic methods (such as iUS, iCT, 5-ALA). According to some authors[2,27] in high-grade gliomas and in metastasis, the tumor displaces the white matter fibers rather than infiltrating them (as opposed to LGGs in which it is possible to localize functional tissue within the tumor[28]); therefore, the functional limit detected by mapping can be considered identical with the anatomical limit of the resection. However, it is common experience that in some cases the resection may be limited by the difficulty of distinguishing neoplastic from healthy brain tissue, thus resulting in STR independently whether it is an eloquent area or not. The need to maximize the rate of radical resection has led to the introduction of intraoperative control methods aimed to distinguish the pathological tissue from the healthy one. The first technological step in this direction was neuronaviagtion, which made possible the localization of even small lesions in subcortical areas. Eisner et al in 2002[29] published the results of surgical treatment of 10 patients affected with subcortical lesions adjacent to the central sulcus by integrating IONM and neuronavigation. However, neuronavigation utilizes preoperative images and it is well known that image-guided surgery based on preoperative images is limited by brain shift. For this reason, intraoperative imaging methods (iUS, iCT, iMRI) and fluorescence-guided surgery with 5-ALA have been introduced. In 2014, we began to perform intracranial surgery using the 3D-iUS-based image guidance system SonoWand. 3D-iUS has the advantage of being a fast, easy-to-use, and inexpensive method, suitable for all types of surgery.[11,12] Literature data suggest that US could detect residual tumor tissue with high specificity and thus improve GTR.[12,30–36] We therefore thought of integratingIONM (which identifies the "functional" limit of resection) with the US data (which identify the "anatomical" limits). The integration of IONM and 3D-iUS acquisitions identifies the eloquent areas in the surgical field, then tumor and the steps of tumor removal. The lesion is to be considered as a volume that occupies the space in its three dimensions. If eloquent motor area is detected at one border of the tumor, the other borders should be free from functional areas and the neurosurgeon can proceed with resection using real-time iUS images, allowing to identify tumor remnants away from the motor areas (►**Fig. 4**). One of the limitations of iUS resection control is the variable pathology's echographic visibility, both at the beginning and during surgery. It is common to observe a reduction of the image quality during the procedure due to surgical artifacts that decrease the US visibility of the lesion and particularly the definition of its edges.[12] The role of 3D US was widely studied by the Trondheim group.[31–33,35] Their studies show that while US is highly accurate in delineating tumors before resection, it appears less accurate during and after that. In fact, during resection there seems to be some overestimation of the tumor, while small tumor remnants and infiltrated tissue in the cavity wall are less clearly seen after resection.[31,35] In our current study, US image quality was considered inadequate to correctly control the resection in eight patients (32%). Overall in four patients (16%), we obtained an STR due to the difficulty of detecting residual lesion despite uneventful IONM. This means that if we had had a more

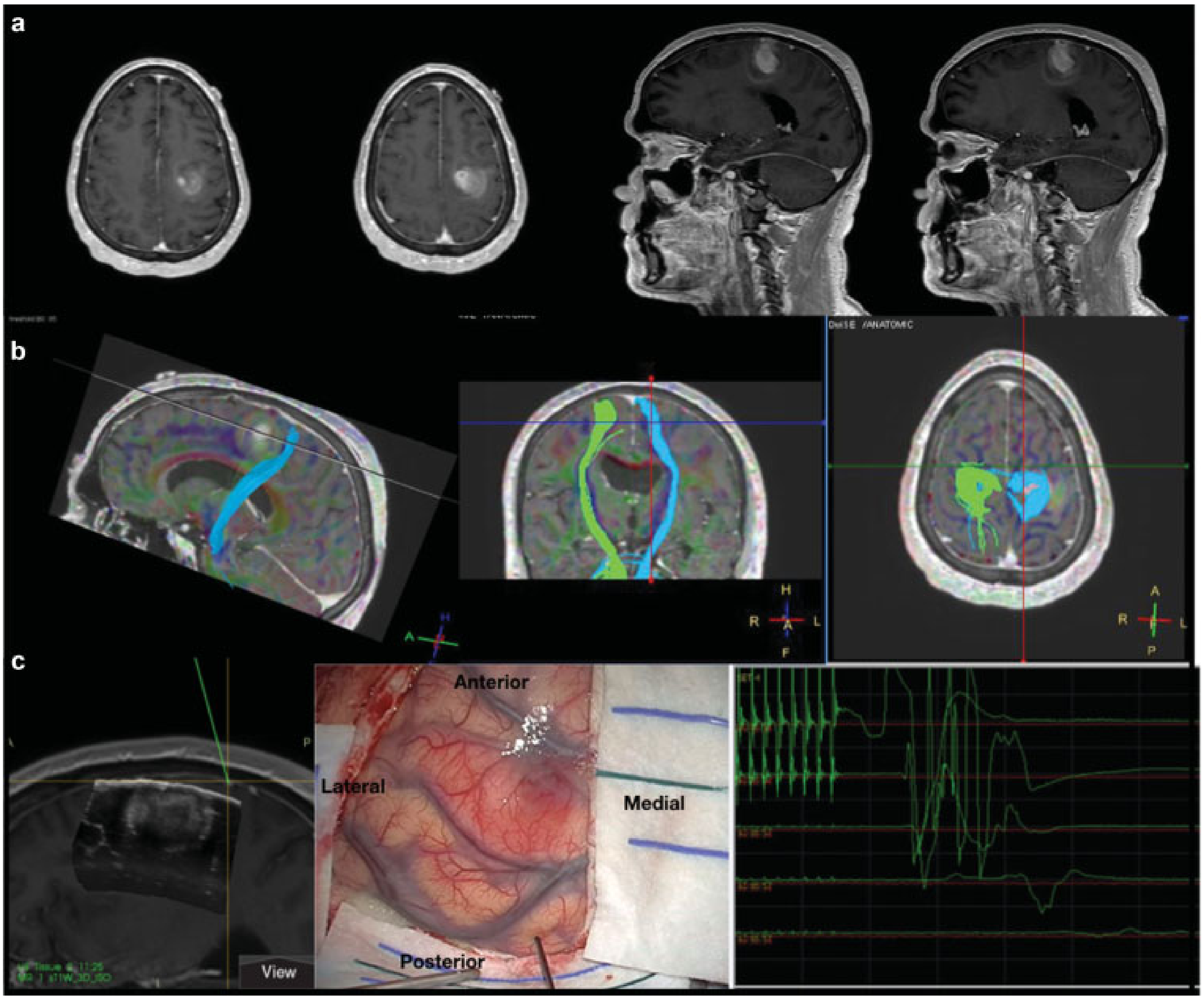

Fig. 4 Patient no. 4. (a) Preoperative T1-weighted magnetic resonance imaging (MRI) with gadolinium showing a left posterior frontal glioblastoma (adjacent to the central sulcus). (b) Tractographic study of the same patient; the tumor displaces the corticospinal tract slightly posteriorly and medially. (c) From left to right: intraoperative ultrasound (iUS) superimposed to the corresponding preoperative MRI; the *yellow crosshair* identifies the position of the stimulating probe; intraoperative picture: the stimulating probe is placed posterior to the tumor. Positive mapping confirming the position of motor area with respect to the tumor. The anterior and lateral margins of the tumor result relatively far from the motor pathway.

reliable method, we could have increased the rate of complete resections. Of 17 patients (68%) with iUS considered persuasive, we obtained 14 GTR confirming the hypothesis that US is useful and improves GTR. We had similar results in our previous experience on 162 patients in whom resection control was found to be persuasive in 83%.[12]

Schucht et al[37] and Feigl et al[38] used neurophysiological mapping during intraoperative 5-ALA-guided resection of GBMs adjacent to motor-eloquent areas. Of 67 patients in the Schucht et al series, complete resection was achieved in 49 (73%), whereas 4% had persisting postoperative motor deficits[37] after 3 months. Similarly, Feigl et al reported GTR in 64% of their 25 procedures and 2 patients with postoperative worsening of the presurgical hemiparesis.[38] The above-mentioned multimodal approach is conceptually similar to ours; it uses the property of 5-ALA to detect tumor remnants with high specificity and therefore enables a more complete resection.[39,40] The fluorescence-guided surgery with 5-ALA is currently considered the most efficacious method to increase the rate of complete resection of high-grade gliomas. Several comparative studies have been done with other methods[41–43](iMRI, iUS), but based on the currently available data, superiority of these techniques over 5-ALA cannot be established.[40–43] 5-ALA seems to identify solid tumor parts and infiltrating tumor cells more accurately than gadolinium-enhanced iMRI sequencies.[41,44] In a recent prospective study, Coburger et al[45] compared the imaging findings of iMRI, 5-ALA, and iUS at 99 intraoperative biopsy sites of 33 GBMs during resection control. All of the assessed imaging techniques detect infiltrating tumor only to a certain extent and only 5-ALA showed a significant correlation with histopathological findings. These data suggest that, at present, 5-ALA is the most effective technique in improving the rate of GTR of GBM; however, it is less specific and nonstandardized for neoplasms like LGG, metastasis, or ependymoma, which could be better approached utilizing other intraoperative techniques (iUS, iMRI, iCT). . Although with its known limitations, intraoperative navigated 3D US can visualize all types of pathologies,[12] and is less expensive compared with iMRI or iCT, has shorter time of acquisition, and does not need special equipment. IMRI is probably more accurate with LGG,[41,46] but a full comparison of the two methods was not the aim of our study.

In our experience, iUS showed low specificity in 8 of 25 patients (32%); on the contrary, IONM turned out to be highly reliable, suggesting that by applying a correct setting (anesthesia and stimulation parameters), negative mapping of eloquent areas provides a safe margin for surgical resection with a low incidence of neurological deficits.[19,20] This allows us to perform a tailored craniotomy to limit the cortical exposure even without localization of the motor cortex. Flap and craniotomy are planned with navigation and in case of negative cortical mapping, the tumor could be approached in a precise and safe trajectory by using iUS.[12,20] Considering the results of our study, as well as the available literature data, we think that our method could be further optimized, first, by lowering the threshold of 6 mA, which is still to be considered too high; Seidel et al[24,47] and Schucht et al,[37] in fact, showed that it is possible to reach a mapping thresholds of 2 to 3 mA without increasing permanent motor deficits. This would lead to an increase in resection near the CST. The optimization of resection, even in the margins not related to the motor areas, can be obtained using the most appropriate methods based on the nature of the pathology: 5-ALA for GBM, iMR for LGG, and iUS for metastases and other lesions. Finally, the above-mentioned methods could also be further integrated in the same procedure: iUS to plan the transcortical trajectory to a deep lesion,[12] 5-ALA to expand the resection of a GBM, and iCT to check the surgical field at the end of the procedure.

Limitations of the Study

Although this is a prospective study, it deals with a small number of patients affected with heterogeneous pathologies. There is no control group. The results appear encouraging and in line with the literature data suggesting the usefulness of multimodal approaches to lesions in eloquent areas. However, a laregr series is necessary for drawing definitive conclusions.Comparison studies with other techniques (such as 5-ALA, iMR) are also required.

Conclusion

We presented a prospective study of 25 patients with cerebral lesions in motor-eloquent areas who underwent surgery by a multimodal approach combining IONM with 3D-iUS-guided resection. Our aim was to obtain a maximal resection with low morbidity. IONM was safe and reliable without false negative results and therefore no unexpected deficit. 3D-iUS was accurate in checking the EOR in 68% of cases identifying residual neoplastic tissue, which was not visible to the “naked eye.” In the remaining cases the lesion margins could not be clearly identified by iUS, either because of the intrinsic low US visibility of the pathology or surgical artifacts. The integration of anatomical and functional data provides the advantages of both techniques and increases the safety of surgery by reducing the risk of permanent neurological deficits without reducing the EOR. Despite encouraging results, this multimodal approach must be validated with broader series as well as with comparative studies comparing this method with other methods.

Informed Consent

All the patients enrolled in the study provided their written consent for anonymous data collection and inclusion in the study

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Conflict of Interest

None declared.

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