© 2016 EDIZIONI MINERVA MEDICA
Online version at http://www.minervamedica.it

Journal of Neurosurgical Sciences 2018 June;62(3):255-64
DOI: 10.23736/S0390-5616.16.03565-7

ORIGINAL ARTICLE

Ultrasound guided mini-invasive tailored approach and intraoperative neurophysiological monitoring: a synergistic strategy for the removal of tumors near the motor cortex. A preliminary experience

Roberto CORDELLA [1] *, Simone NAVA [2], Francesco PRADA [1], Alessandro AGNOLETTI [3], Federico LEGNANI [1], Francesco DIMECO [1]

[1]Department of Neurosurgery, IRCCS Neurologic Institute "C. Besta" Foundation, Milan, Italy; [2]Department of Neuroradiology, IRCCS Neurologic Institute "C. Besta" Foundation, Milan, Italy; [3]Division of Neurosurgery, Department of Neuroscience, Molinette Hospital, University of Turin, Turin, Italy

*Corresponding author: Roberto Cordella, Department of Neurosurgery, Fondazione IRCSS Istituto Neurologico C. Besta, Via G. Celoria 11, 20133 Milan, Italy. E-mail: rcordella@istituto-besta.it

ABSTRACT

BACKGROUND: The aim of this paper was to evaluate the synergic strategy comprising intraoperative neurophysiological monitoring and ultrasound sonography in terms of clinical motor scores and extent of resection.
METHODS: Patients harboring tumors in close relationship with the motor cortex were operated on with image-guided mini-invasive approach and multimodal neurophysiological monitoring. The peculiarity is the partial exposure of the motor cortex and the limited electrophysiological mapping used to search for negative spots. Multimodal neurophysiological monitoring comprised the electrocortical stimulation, somatosensory evoked potentials, motor evoked potentials and subcortical stimulation. Ultrasound sonography guided the tumor removal. The post-op clinical motor scores and the extent of resection were assessed.
RESULTS: Twelve patients were operated on with the combined approach and were further analyzed. Six had high grade gliomas, 1 anaplastic astrocytoma, 1 oligodendroglioma, 1 pilocytic astrocytoma and three had metastasis. One out of 12 had a worsening of the motor scores at the last follow-up. The mean extent of resection was 90% ranging from 60% to 100%, but in 9 out of 12 patients, it reached or exceeded 90%.
CONCLUSIONS: The synergic strategy comprising intraoperative multimodal neurophysiological monitoring and the ultrasound sonography is feasible in all surgeries. Data are promising in terms of both clinical motor scores and extent of resection. This strategy represents an alternative approach to the treatment of supratentorial tumors, although further studies are necessary to confirm the long-term efficacy of this procedure.

(*Cite this article as:* Cordella R, Nava S, Prada F, Agnoletti A, Legnani F, DiMeco F. Ultrasound guided mini-invasive tailored approach and intraoperative neurophysiological monitoring: a synergistic strategy for the removal of tumors near the motor cortex. A preliminary experience. J Neurosurg Sci 2018;62:255-64. DOI: 10.23736/S0390-5616.16.03565-7)

Key words: Brain neoplasms - Neurophysiology - Motor cortex - Ultrasonography.

Supratentorial tumors in close spatial proximity with eloquent areas represent a major challenge for neurosurgeons. The aim is maximal removal of the tumor without decreasing the patients' quality of life. Technological advances comprising of fMRI scans, intraoperative neuro-navigators, and neurophysiological monitoring techniques are pivotal in managing supratentorial tumors in close spatial proximity with eloquent areas. These imaging techniques help with the preoperative planning of the surgical strategy, while during surgery, they indicate tumor boundaries and the relationships of the tumor with nearby vital structures, thus enhancing precision, accuracy, and safety for the patients and allowing for maximal resection. Direct electrocortical stimulation (ECS) is the gold standard for the recognition of the eloquent parenchyma, motor and language, through the detection of neurological responses by means of either EMG recordings or neuropsychological evaluation in awake patients.[1-4] Multimodal intraoperative neurophysiological monitoring (IOM) has proven to be effective in preventing new unwanted neurological impairments during surgery in eloquent areas in standard neurosurgical approach [5, 6] and also in image-guided mini-invasive neurosurgery.[7] In addition, IOM allows to assess continuously the motor functions without interrupting the surgical flow.

Uploading MRI and fMRI scans into the intraoperative neuro-navigation system should be considered mandatory for the planning and execution of surgical procedures. However, both techniques are based on imaging acquired preoperatively and as a main limitation, their accuracy decreases during the course of the surgical manipulation due to the phenomenon known as brain shift.[8] Brain shift is caused by multiple factors such as the effect of the gravity on the brain, brain swelling, leak of cerebrospinal fluids and surgical maneuvres.[9, 10] Intraoperative MRI, CT [11, 12] and ultrasonography [13] are the only methods available to gain intraoperative information on brain shift. Technological advances have continued to improve the value of intraoperative ultrasound (iUS) by integrating it with neuroimaging systems currently used during surgery.[14]

The combination of IOM and ultrasound scans might be pivotal in limiting the incidence of unwanted neurological deficits post-operatively and increasing the amount of gross total resection. This study evaluates our results of supratentorial tumors resection achieved with the combination of IOM and neuronavigated ultrasound sonography. Indexes such as clinical scores and amount of resection have been assessed to understand the impact of the combination of these two techniques in neurosurgical practice.

Materials and methods

Patients and clinical assessment

The study enrolled patients who underwent elective surgery with tailored mini-invasive image-guided craniotomy to remove tumors nearby the motor cortex and tract with the aid of iUS and IOM. Image-guided surgical approach comprises the planning of the trajectory with the aid of the standard neuronavigation system and US-guided neuronavigation to assess the tumor's boundaries during the removal. A decision to perform a mini-invasive surgical approach, by linear incision and small craniotomy, was made based on tumor characteristics. The latter were: 1) maximum tumor diameter less than 4 cm; 2) cortical spatial direct relationship with the motor cortex as evaluated by fMRI; 3) none or minimal superficial extension of the lesion in contact with the pre-motor, motor or parietal cortices.[7] All patients were pre- and postoperatively assessed (1-week- and 3-month-follow-up), according to a standard protocol, and muscle strength was graded on a 0-V scale (0: no movements; I-II: severe paresis; III-IV: moderate paresis; V: normality) British Medical Research Council Scale (BMRC).[15]

The Institutional Review Board approved the study and all patients gave written informed consent prior to the surgery.

Surgical technique and ultrasound procedure

MRI-based surgical planning with neuronavigation was performed. MRI was coupled with US system equipped with Virtual Navigator (MedCom, Darmstadt, Germany) software for Fusion Imaging, allowing real-time neuronavigation between preoperative MRI and real-time US. All procedures were performed under general anesthesia, and an image-guided mini-invasive approach was performed that included linear skin incision, followed by one burr hole and a small craniotomy (Figure 1) centered on the pre-planned trajectory to the tumor. The size of the craniotomy was just big enough to allow to the smallest probe to move in all directions. Ultrasound evaluation of the lesion was performed prior to and following the dural opening (Figure 1), as re-

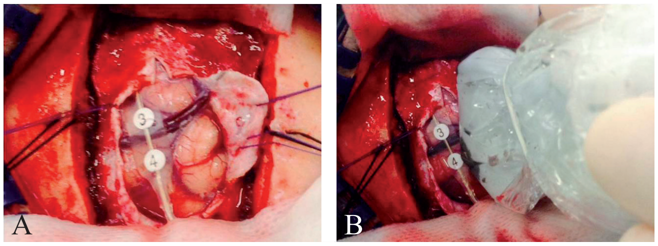

Figure 1.—Illustrations of the planned craniotomy and its diameter showing the insertion of the 4 contacts strip electrode underneath the dura (A) and the Ultrasound evaluation of the lesion following the dural opening (B).

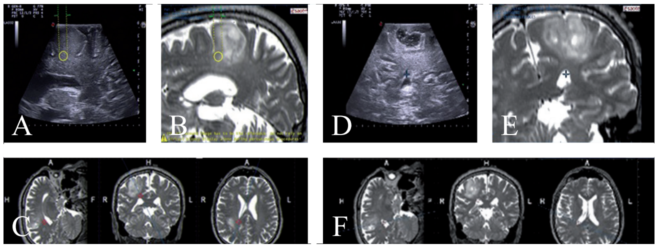

Figure 2.—Intraoperative fusion imaging (real-time ioUS and pre-operative MRI) findings. Preresection sagittal section displaying US findings (A) with an hyper echoic area showed by the pointer tip (cylinder) and corresponding co-planar preoperative MRI findings (B). In D the postresection US imaging is showed, along with the corresponding preoperative MRI (E), providing further orientation and help in interpreting the imaging. C and F shows the probe position in the three traditional orthogonal planes.

ported in previous studies by our group. After bone flap removal, a 3- to 11-MHz linear US navigated probe (Esaote, Genoa, Italy) was placed in a surgical sterile transparent plastic sheath, along with 5-mL US transducing gel. The probe was placed over the dura to acquire standard B-mode imaging scans. The lesion was identified on the 2 axes and then measured.[16]

All lesions were initially evaluated with B-mode imaging, and a morphological qualitative online intraoperative assessment was performed: in particular, it was evaluated tumor gray scale intensity and texture, superficial arachnoidal and deep white matter margins, perilesional edema compared to apparently healthy brain tissue (Figure 2). All lesions were defined as highly hyperechoic, mildly hyperechoic, or isohypoechoic compared with the surrounding normal brain parenchyma. Other lesion features considered were the presence of calcification, and either cystic or necrotic areas. In order to have a clearer understanding, US imaging was correlated with the navigated co-planar preoperative MRI. All data obtained by US analyses was correlated with the histopathology of each lesion.

As a consequence of the small craniotomies (Figure 1) tailored on the tumor, the motor cortex is exposed partially or not at all, and indeed an IOM protocol including a limited ECS in the search of negative spots (*i.e.* non eloquent cortex) and a multimodal monitoring had been employed.

Following dural opening, the 4-contact strip electrode (Integra Corporation, MN, USA) — to record electrocorticography, SSEP and direct motor evoked potentials — was carefully introduced underneath the dura (Figure 1) towards the motor strip and positioned onto the targeted area according to neuronavigation and electrophysiological data. Subsequently, the surgeon performed a neurophysiological mapping by stimulating the tumor and the surrounding cortex looking for negative and positive responses.

MR imaging and assessment of tumor volume

Patients underwent a conventional MRI protocol pre- and postsurgery either at the 1.5 Tesla.

(Siemens Avanto, Erlangen, Germany) or 3 Tesla (Philips Achieva, Best, the Netherlands) site. Postoperative MRI was achieved within 72 hours from the surgical procedure.

High-resolution sequences were acquired for neuronavigation: volumetric fast-field echo (FFE) T1-weighted MR images (TR/TE: 1160/4.24 msec; 192 sections with a 0.9x0.9x0.9 mm^3 nominal resolution and 0.45 mm interslices gap) for 1.5T, and volumetric turbo-field echo (TFE) T1-weighted MR images (TR/TE: 7.16/3.21 msec; 192 sections with a 1x1x1 mm^3 nominal resolution and 1 mm interslices gap) for 3T, following intravenous administration of the contrast agent. In addition, axial T2-weighted and fluid attenuated inversion recovery (FLAIR) were acquired. Tumor boundaries, as well as post-operative residuals, were identified and segmented on the volumetric T1 sequences on every axial slice in order to accurately compute their volume with Osirix imaging software v. 3.1.[17] For a higher reliability, correspondent T2 and FLAIR sequences were simultaneously loaded and inspected. Extent of resection (EOR) was computed by a volume subtraction approach between preoperative mass and postoperative residual.

IOM

Electroencephalography and electrocorticography

Both signals monitored brain oscillatory activity and the related states (*i.e.* delta, theta oscillations). Electroencephalography (EEG) was used to monitor brain areas when electrocorticography (ECoG) is not available (*i.e.* start and end of the surgery, bad signals of the ECoG electrodes), to monitor the effect of anesthetic drugs, and to detect seizures. ECoG was recorded to direct assess brain activity and to define the working current through the detection of after discharges and subclinical seizures. The occurrence of epileptic seizures was managed through immediate cortical irrigation with cold-saline solution and antiepileptic drugs (AEDs). EEG was recorded bilaterally with subdermal needle electrodes using C3'-C4'-T3-T4 of the International 10-20 System, all referred to a midfrontal site, similarly ECoG was arranged in a monopolar array (midfrontal cathode as reference). Both signals were recorded with a bandpass filter set from 1 to 70Hz, and sensitivity of 200 µv division.

ECS and free run EMG

The surgeon performed the direct electrical stimulation through a hand-held bipolar probe. This methodology was used to confirm that the planned trajectory do not comprise eloquent cortex. Thus, ECS was performed stimulating the tumor and surrounding cortex looking for negative and positive responses.

Evoked responses were recorded on free run EMG. The stimulation parameters were from 1 to 10 mA intensity, 60Hz frequency and 1 ms pulse-width. Free run EMG was recorded through two subdermal monopolar stainless steel needles, 2 cm apart from one another. The *orbicularis oris*, wrist extensor, deltoid, triceps, *abductor pollicis brevis*, *abductor digiti minimi*, *rectus femori*, *tibialis anterior* and *extensor digitorum brevi* were the muscles selected to monitor the contralateral hemisoma. Free run EMG was recorded with a band pass of 40-1000Hz.

Somatosensory evoked potentials

Somatosensory evoked potentials (SSEPs) of the contralateral — to the lesion side — median nerve stimulation were performed to localize the central sulcus through the N20 phase inversion (P20). In addition a C3'/C4' contact of the International 10-20 System (approximately 7-7.5 cm lateral and 2 cm behind from the midline on the central sulcus line) to record scalp evoked potentials was used as a reference and compared to the P20. Between 100 and 200 traces were averaged for optimizing

Table I.—*Patients' data, the extent of resection and the comparison between preoperative and postoperative clinical motor score.*

Patient	Age at surgery (years)	Gender	Histopathology	Tumor location	EOR (%)	Preoperative symptoms (BMRC score)	Postoperative symptoms 3 months FU (BMRC score)
1	58	M	Metastasis	Frontal	95.69	Seizures and upper limb paresis (3)	No new deficits (3)
2	59	M	Glioblastoma	Frontal	76.79	Seizures (5)	Hemiparesis (3)
3	20	M	Pilocytic astrocytoma	Frontal	95.79	Asymptomatic (5)	No new deficits (5)
4	60	F	Metastasis	Frontal	96.92	Aphasia and seizures (5)	No new deficits (5)
5	52	M	Glioblastoma	Fronto-parietal	95.76	Seizures (5)	No new deficits (5)
6	20	F	Anaplastic astrocytoma	Frontal	93.89	Seizures (5)	No new deficits (5)
7	31	M	Oligoastrocytoma	Frontal	89.67	Seizures (5)	No new deficits (5)
8	27	F	Glioblastoma	Frontal	100.00	Seizures (5)	No new deficits (5)
9	38	M	Glioblastoma	Fronto-parietal	61.51	Seizures and upper limb paresis (4)	No new deficits (4)
10	63	F	Glioblastoma	Parietal	76.71	Aphasia and hemiparesis (2)	No new deficits (2)
11	64	M	Metastasis	Fronto-parietal	100.00	Seizures (5)	No new deficits (5)
12	58	F	Glioblastoma	Frontal	100.00	Upper limb paresis (3)	No new deficits (3)
Mean	46				90.23		

BMRC: British Medical Research Council; EOR: extent of resection; FU: follow-up.

the signal-to-noise ratio. The presence of P20 was related to the positioning of the contact on the motor cortex and the central sulcus. Stimulation parameters were: intensity ranging from 20 to 30 mA, 3 Hz rate and 20 ms pulse width. Band-pass filter was set from 5 to 2000 Hz.

Direct motor evoked potentials

Direct motor evoked potentials (dMEP) has allowed the real time continuous monitoring the lower limb motor functions during the tumors removal. Monopolar stimulation (midfrontal site as cathode) was performed using only those strip electrode contacts showing P20. Stimulation was performed by short train of stimuli (3 to 5) consisting of rectangular pulses with a pulse width of 0.5-1.0 ms, and a bandpass filter set from 30 to 3000Hz. Responses were detected from the same group of muscles reported for the free run EMG. A 50% decrease in amplitude in more than three consecutive responses was set as the warning criterion, as well as an increase in stimulation amplitude above 20%.[18, 19]

Subcortical stimulation

Monopolar subcortical stimulation (Fpz as cathode) was performed to estimate the distance between the stimulating point and the corticospinal tract. The parameters were as follows: short train of stimuli (3 to 5) consisting of rectangular pulses with a pulse width of 0.5-1.0 ms and intensity up to 20 mA. The evoked responses were detected on the EMG.

Anesthesia protocol

During the entire surgical session, all patients were under general anesthesia with propofol target control infusion (TCI) as primary choice, because it has been shown to produce a more stable neurophysiological environment for monitoring, than inhalational anesthetics.[20-23] The main advantage of this methodology is a prompt response to signs of inappropriate anesthesia depth without any need for mathematical calculations.[24] TCI effect compartment concentration (Ce) during the maintenance was performed using Schnider's model [25] for Propofol and Minto's model [26] for remifentanil. During the procedure, the depth of the anaesthesia was assessed continuously through the bispectral index (BIS Vista, Aspect Medical Systems, Newton, MA, USA) targeted between 40 and 60.[27] Muscle relaxants were administered for intubation purposes only and were not used during the entire surgical session.

Results

Patients' description

Twelve patients that were operated on with the mini-invasive image-guided tailored craniotomy with the aid of ultrasound and IOM met the inclusion criteria and were further analyzed. Seven patients were males and 5 females, having a mean age at surgery of 42±12 years (range 12-64). Seven patients harbored lesions on the right hemisphere and 5 harbored lesions on the left. Preoperative symptoms comprised of generalized seizures in 6 patients, hemiparesis contralateral to the lesion in 2, seizures and hyposthenia in 1, seizures and aphasia in 1, aphasia and hemiparesis in 1, and one was asymptomatic. Preoperative BMRC scores were grouped as follows: seven had 5, two had 4, two had 3 and one had 2 (Table I). Seven patients were under AEDs either to prevent or control seizures. Histological diagnosis was glioblastoma multiforme in 6 patients (World Health Organization – WHO grade IV), 1 anaplastic astrocytoma (World Health Organization – WHO grade III), 1 oligodendroglioma (WHO grade II), 1 pilocytic astrocytoma (WHO grade I), and metastatic tumors in 3 (Table I).

Electrophysiological findings

N20 phase inversion

Primary motor area (Brodmann's area 4) localization through N20 phase inversion (P20) was achieved in all surgeries (Figure 3A), although in three procedures the position was refined in accordance to the electrophysiological results (Table II). In these three latter procedures the first strip's position displayed N20 in all contacts, indicating that the contacts were located in the somatosensory cortex.

ECS

ECS was performed in all procedures. Stimulation amplitude ranged from 4 to 7mA. At least 5 cortical spots (range 5-7) per patient were stimulated and mus-

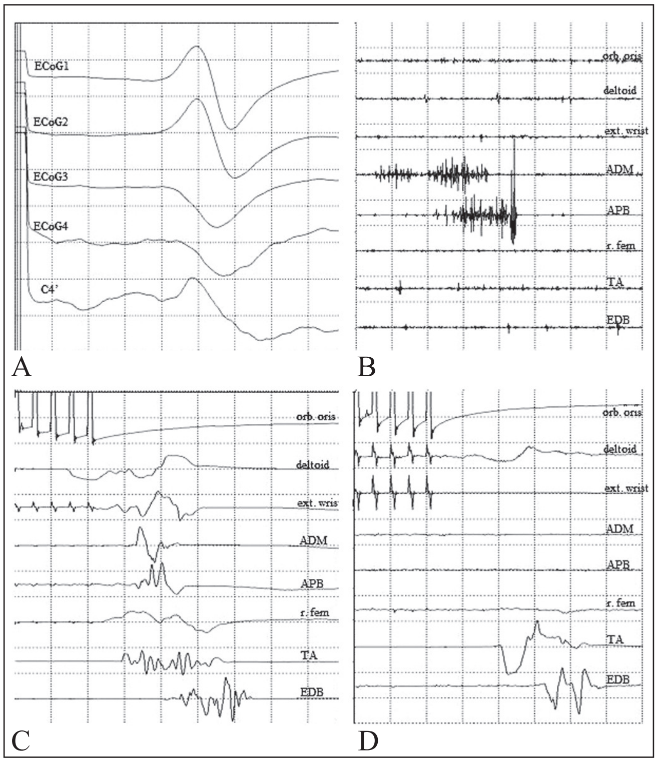

Figure 3.—Multimodal IOM comprises EEG and ECoG (both not shown) and A) SSEP, illustrating the N20 (on ECoG1, ECoG2 and C4') and the P20 (on ECoG3 and 4). This result informed that the strip was located on the motor cortex (ECoG3 and 4) and on the somatosensory cortex (ECoG 1 and 2), indeed the former contacts were used to evoke dMEP; B) EMG, showing activation of the hand's muscles (*abductor pollicis brevis* and *abductor digiti minimi*) during ECS mapping; C) dMEP evoked through one of the two contacts of the strip electrode; D) subcortical mapping activating the lower limb muscles.

cle contractions were recorded in only two patients (one upper limb and one lower limb) (Figure 3B). In one of these two patients a stimulus-evoked generalized seizure was documented that was halted through the irrigation of the exposed cortex with ice-cold saline solution.

dMEP and subcortical stimulation

dMEP through monopolar stimulation by mean of the strip's contacts showing the phase inversion was achieved in all procedures with a maximal of 20 mA anodal stimulation (Figure 3C). At the end of the procedure, in none of the patients has been recorded a decrease of the response wider than the 50% of the baseline. Subcortical stimulation was performed in only two patients (Figure 3D). In one patient, subcortical stimulation was positive with intensities around 10mA, while in the other the lower intensity was 5 mA (Table II).

Clinical findings

At the 1-week follow-up, 3 out of 12 patients (25%) experienced a worsening of the preoperative symptoms. Specifically one patient had a BMRC score dropping from 5 to 1, one from 4 to 2 and the one from 3 to 1. All three patients underwent rehabilitative physical activity. At the 3-month follow-up the preoperative BMRC scores were restored in the latter two, while in the former the BMRC score at this follow-up was 3 (Table I).

Radiological findings

The mean EOR for the group of patients was 90% (Table I). Resections ranged from 62% to 100%, but in 9 out of 12 patients, it reached or exceeded 90%. Subtotal resection was achieved in the remaining 3 cases,

Table II.—*Electrophysiological results.*

Patient	N20 Phase reversal	ECS total	ECS Positive/ negative	EEG/ECoG findings	Subcortical stimulation (lower intensity)
1	Yes (position refined)	5	0/5	Afterdischarge	No
2	Yes	7	1/5 (upper limb)	Seizures (also clinical)	Yes (5mA)
3	Yes	5	0/5	No seizures	No
4	Yes	5	0/5	No seizures	No
5	Yes	5	0/5	No seizures	No
6	Yes (position refined)	5	1/5 (lower limb)	No seizures	No
7	Yes (position refined)	5	0/5	Seizures ECoG (no clinical)	No
8	Yes	6	0/6	No seizures	No
9	Yes	5	0/5	No seizures	No
10	Yes	5	0/5	No seizures	No
11	Yes	6	0/6	No sezures	Yes (10mA)
12	Yes	5	0/5	No seizures	No
Mean	46				

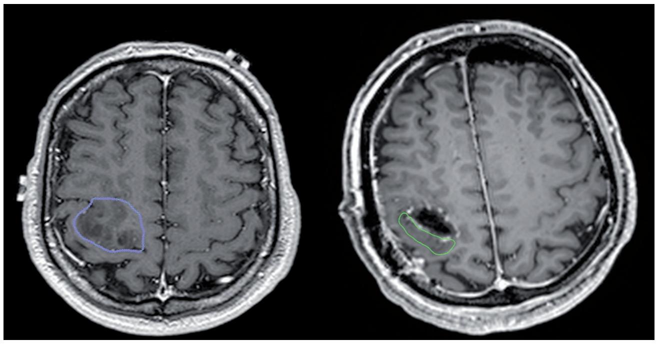

Figure 4.—Postoperative contrast-enhanced T1 MR image (on the right side) shows the tumor residual outline, compared with pre-op lesion outline (on the left). In this patient (#2) the dramatic spatial correspondence of the tumor mass with the eloquent motor cortex, positively responsive to ECS, led to the decision to exclude the outlined portion from resection. EOR was hence subtotal (76.8%).

due to the close spatial relationship between pathological tissue and motor structures (Figure 4), identified by either cortical or subcortical stimulation.

Discussion

This report describes the combined use of multimodal neurophysiological monitoring and neuronavigated ultrasound sonography during image-guided mini-invasive tailored approach neurosurgical procedures for tumor removal in motor areas. The aim is to apprehend the value of the combined approach in terms of extent of tumor resection and post-op clinical scores. The peculiarity is the mini-invasive approach which is based on an image-guided tailored approach to target the pathology, while minimizing the trauma to the surrounding healthy nervous system and other functional structures.[28, 29] The consequence is that the motor area is not mapped through direct ECS and indeed it has been necessary to achieve its spatial relationship with the tumor indirectly.[7] This goal has been pursued through the search of the negative cortical spots [3] and by means of SSEP.[30-32] Specifically, the stimulated spots were the tumor and the surrounding regions with the goal to not evoke EMG, whereas the N20 phase reversal, namely the P20, suggested the anatomical location of the motor cortex. This electrophysiological potential is index of the placement of the recording sites on the central sulcus and motor cortex.[33, 34] The initial cortical component of the SSEP to median nerve stimulation is typically recorded as a negativity, labelled N20, over the parietal scalp contralateral to the stimulated nerve. A positivity of similar latency, labelled P20, is often recorded over the frontal area of the same hemisphere.[31, 32] Following the electrophysiological mapping, tumor resection is accomplished under the guidance of the ultrasound sonography, and the preservation of the corticospinal tract is monitored through dMEP. The data points out that the mean extent of resection was 90% associated with a postoperative clinical score worsening in 1 out of 12 patients. Interestingly, this patient is the only one where the ECS evoked a seizure and the ECS was positive, and indeed it has been decided to limited the resection of the infiltrated brain tissue to avoid permanent plegia.

Similarly, positive ECS and subcortical mapping was also seen in both patients in whom the EOR was around 60%, although the motor scores at the last follow-up were equal to the preoperative period.

The search of a solid methodology in the removal of glial tumors in close spatial relationship with eloquent areas with the maximal extent of resection possible with less morbidity represents a major challenge for modern neurosurgery. In recent years, the correlation between EOR and patients' overall survival has been investigated resulting in the finding that the former affects the latter.[35] Furthermore, the use of combined approaches, such as intraoperative MRI, fluorescence guided surgery, intraoperative neurophysiology and neuronavigation amongst the many, might affect EOR.[36] MRI-based neuronavigation associated with IOM has been found to correlate with extent of resection and with favorable clinical results.[37] However, this combination did not take into account the magnitude of the brain shift which might hamper the reliability of MRI based neuronavigation, thus it might hamper the amount of tumor resection. According to a recent review, the current evidence supports the use of DTI functional neuronavigation, intraoperative MRI and IOM as tools for improving EOR.[36] Promising results have been reported with the combined use of these techniques.[38, 39]

Moreover, iUS has been investigated as an intraoperative assistive technology in neurosurgery. iUS's main advantage is the ability to evaluate the extent of resection in real time and not on a previous image that does not correspond to the intraoperative reality. This means that during surgery the brain shift and the resection might modify the shape of the brain and consequently do not match with preoperative images. Ohue *et al.*[40] have illustrated the amount of brain shift during neurosurgical procedures by means of iUS. The brain shift is already detectable before the dural incision, increases before tumor removal and reaches its maximum during and after the removal. Indeed iUS should allow to continuously correct brain displacement that with which standard neuronavigation systems do not identify. Furthermore, as described in other paper from our group, when dealing with lesions located close to eloquent areas, not only brain shift should be taken into account but also tissue deformation due to tumor removal and parenchyma manipulation. When this occurs, the possibility to compensate these changes relying on intraoperative ultrasound to recalibrate neuronavigation, especially if it contains functional data, is of pivotal importance.[41] Moreover, it has been shown how iUS is very useful in evaluating the location, defining the border, and depicting the vascularization and perfusion pattern of various brain tumors. Especially in tumors with ill-defined borders such as gliomas, iUS was very helpful in highlighting the lesion and its boundaries and possibly differentiating between tumor/edematous brain tissue. Moreover, it has been demonstrated the ability of iUS to highlight vascular structures that make it easier for the surgeon to identify the vascular peduncles, giving further insight to the surgical strategy, such as facilitating vascular deafferentation of the lesion and then its surgical removal.[16] After gross tumor removal, iUS might also be used to highlight tumor remnants, thus maximizing resection and avoiding neurological sequelae resulting from damaged healthy brain tissue. Furthermore, iUS is a readily repeatable, dynamic, inexpensive procedure that can be performed any time for a potentially unlimited number of times during surgery.[42] Moreover, it might be employed in all those centers that have not the possibility to use intraoperative MRI.

Different imaging modalities should be used, when available, with a synergistic approach. For example, 5-ALA and iUS represents two different ways to look at the same problem and are in fact complementary, rather than in competition: 5-ALA is a metabolic-optical imaging modality, which shows pathologic tissue on the directly visible surface, whereas ultrasound is a real-time imaging modality able to show a tomographic section of the surgical field. In our opinion the two modalities should be used in a synergistic fashion in order to exploit their potential at best.

The combination of iUS and IOM is poorly described. Introductory attempts to shed light to the usefulness of the joint usage of iUS and IOM have been presented by King and Shell [30] and Firsching *et al.*[43] Both investigations have stated that SSEP and MEP allowed to identify the sensory-motor boundaries and the spatial relationship with the tumors, aiding the surgical strategies with tolerable postoperative neurological impairments. In recent times, Nossek *et al.*[14] has described the combination of multimodal IOM and iUS in both awake and general anesthesia procedures. The authors stated that gross total resection was achieved in 11 out of 16 patients and in almost 13% of the patients there were worsening long term motor scores. Interestingly, they did not find statistical differences between awake and under general anesthesia procedures. Unfortunately, the amount of resection was not the main goal of the authors and indeed detailed analyses are not described. Despite this limitation, the comparison of Nossek *et al.*[14] and our data suggests a substantial similarity in extent of resection and post-op motor scores.

Limitations of the study

There are a few limitations of this study that need to be recognized. The main limitation is the small sample size. This limited the possibility to draw solid conclusions that might be generalized. Another limitation arises with the heterogeneity of the populations. More consistent conclusions might be drawn with homogeneous groups such as either low-grade or high-grade gliomas, metastasis etc. The combined approaches bear the limitation that it is difficult to assess the contribution of each technique to the planned outcomes, indeed prospective studies using correct multivariate analyses might be conducted to evaluate the impact of each employed technique. However the aim of this report is to investigate the feasibility of these specific combined methods in a peculiar neurosurgical plan, namely the image-guided mini-invasive neurosurgery with consideration to the EOR and neurological outcomes. It is worthy to state that image-guided mini-invasive neurosurgical approach might be planned by a well-trained group that has experience not only in oncological procedures but also in functional and cerebrovascular procedures. The data are promising, whereas despite the narrow craniotomies and the indirect detection of the motor areas placement, both IOM and iUS were feasible in all procedures, gave positive feedback to the surgeons, guiding the tumor removal with encouraging results.

Conclusions

In this study it has been investigated the extent of resection and the clinical motor scores in patients who underwent image-guided mini-invasive neurosurgery, employing iUS and multimodal neurophysiological monitoring for the removal of lesions in the nearby of the motor cortex. Data are encouraging, with a mean extent of resection around 90%. Only one patient did experience worsening of the postoperative motor scores. Ultrasound sonography allows to correct brain shift during the procedure helping the surgeon in the search of radicalness, while multimodal IOM allows to constantly monitor the motor functions lessening the morbidity.

References

1. Cordella R, Acerbi F, Marras CE, Carozzi C, Vailati D, Saini M, *et al.* Risk of seizures during intraoperative electrocortical stimulation of brain motor areas: a retrospective study on 50 patients. Neurol Sci 2012;34:63-70.
2. Duffau H. Contribution of cortical and subcortical electrostimulation in brain glioma surgery: methodological and functional considerations. Neurophysiol Clin 2007;37:373-82.
3. Sanai N, Berger MS. Intraoperative stimulation techniques for functional pathway preservation and glioma resection. Neurosurg Focus 2010;28:E1.
4. Szelényi A, Bello L, Duffau H, Fava E, Feigl GC, Galanda M, *et al.* Workgroup for Intraoperative Management in Low-Grade Glioma Surgery within the European Low-Grade Glioma Network: Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. Neurosurg Focus 2010;28:E7.
5. Bertani G, Fava E, Casaceli G, Carrabba G, Casarotti A, Papagno C, *et al.* Intraoperative mapping and monitoring of brain functions for the resection of low-grade gliomas: technical considerations. Neurosurg Focus 2009;27:E4.
6. Kombos T, Picht T, Derdilopoulos A, Suess O. Impact of intraoperative neurophysiological monitoring on surgery of high-grade gliomas. J Clin Neurophysiol 2009;26:422-5.
7. Cordella R, Acerbi F, Broggi M, Vailati D, Nazzi V, Schiariti M, *et al.* Intraoperative neurophysiological monitoring of the corticospinal tract in image-guided mini-invasive neurosurgery. Clin Neurophysiol 2013;124:1244-54.
8. Kelly PJ, Kall BA, Goerss S, Earnest FIV. Computer-assisted stereotaxic laser resection of intra-axial brain neoplasms. J Neurosurg 1986;64:427-39.
9. Hill DL, Maurer CR Jr, Maciunas RJ, Barwise JA, Fitzpatrick JM, Wang MY. Measurement of intraoperative brain surface deformation under a craniotomy. Neurosurgery 1998;43:514-28.
10. Obuchi T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Yamamoto T. Direction and predictive factors for the shift of brain structure during deep brain stimulation electrode implantation for advanced Parkinson's disease. Neuromodulation 2008;11:302-10.
11. Maurer CR Jr, Hill DL, Martin AJ, Liu H, McCue M, Rueckert D, *et al.* Investigation of intraoperative brain deformation using a 1.5-T interventional MR system: preliminary results. IEEE Trans Med Imaging 1998;17:817-25.
12. Nimsky C, Ganslandt O, Cerny S, Hastreiter P, Greiner G, Fahlbusch R. Quantification of, visualization of, and compensation for brain shift using intraoperative magnetic resonance imaging. Neurosurgery 2000;47:1070-80.
13. Jödicke A, Deinsberger W, Erbe H, Kriete A, Böker DK. Intraoperative threedimensional ultrasonography: an approach to register brain shift using multidimensional image processing. Minim Invasive Neurosurg 1998;41:13-9.
14. Nossek E, Korn A, Shahar T, Kanner AA, Yaffe H, Marcovici D, *et al.* Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation. Clinical article. J Neurosurg 2011;114:738-46.
15. Medical Research Council. Aids to the examination of the peripheral nervous system, Memorandum no. 45. London: Her Majesty's Stationery Office; 1981.
16. Prada F, Mattei L, Del Bene M, Aiani L, Saini M, Casali C, *et al.* Intraoperative cerebral glioma characterization with contrast enhanced ultrasound. Biomed Res Int 2014;484261.
17. Rosset A, Spadola L, Pysher L, Ratib O. Informatics in radiology (infoRAD): navigating the fifth dimension: innovative interface for multidimensional multimodality image navigation. Radiographics 2006;26:299-308.
18. Neuloh G, Pechstein U, Cedzich C, Schramm J. Motor evoked potential monitoring with supratentorial surgery. Neurosurgery 2004;54:1061-70.
19. Neuloh G, Schramm J. Motor evoked potential monitoring for the surgery of brain tumors and vascular malformations. Adv Tech Stand Neurosurg 2004;29:171-228.
20. Nathan N, Tabaraud F, Lacroix F, Moulies D, Viviand X, Lansade A, *et al.* Influence of propofol concentrations on multipulse transcranial motor evoked potentials. Br J Anaesth 2003;91:493-97.
21. Pechstein U, Nadstawek J, Zentner J, Schramm J. Isoflurane plus nitrous oxide versus propofol for recording of motor evoked potentials after high frequency repetitive electrical stimulation. Electroencephalogr Clin Neurophysiol 1998;108:175-81.
22. Pelosi L, Stevenson M, Hobbs GJ, Jardine A, Webb JK. Intraoperative motor evoked potentials to transcranial electrical stimulation during two anaesthetic regimens. Clin Neurophysiol 2001;112:1076-87.
23. Wang AC, Than KD, Etame AB, La Marca F, Park P. Impact of anesthesia on transcranial electric motor evoked potential monitoring during spine surgery: a review of the literature. Neurosurg Focus 2009;27:E7.
24. Holas A. A total intravenous anesthesia: Target-controlled anesthesia; 2005 [Internet] Available from http:/ /www.anesthesia.at/anesthesiology.tiva3.html [cited 2005, May 21].
25. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, *et al.* The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90:1502-16.
26. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil: II. Model application. Anesthesiology 1997;86:24-33.
27. Gale T, Leslie K, Kluger M. Propofol anesthesia via target controlled infusion or manually controlled infusion Effects on the bispectral index as a measure of anesthetic depth. Anaesth Intensive Care 2001;29:579-84.
28. Perneczky A, Muller-Forell W, van Lindert E, Fries G. Keyhole concept in neurosurgery. Stuttgart, New York: Thieme Medical Publishers; 1999.
29. Reisch R, Perneczky A. Ten-year experience with the supraorbital subfrontal approach through an eyebrow skin incision. Neurosurgery 2005;57:242-55.
30. King RB, Schell G. Cortical localization and monitoring during cerebral operations. J Neurosurg 1987;67:210-9.

31. Lüders H, Dinner DS, Lesser RP, Morris HH. Evoked potentials in cortical localization. J Clin Neurophysiol 1986;3:75-84.
32. Wood CC, Spencer DD, Allison T, McCarthy G, Williamson PD, Goff WR. Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg 1988;68:99-111.
33. Desmedt JE, Nguyen TH, Bourguet M. Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses. Electroencephalogr Clin Neurophysiol 1987;68:1-19.
34. Gregorie EM, Goldring S. Localization of function in the excision of lesions from the sensorimotor region. J Neurosurg 1984;61:1047-54.
35. Sanai N, Berger MS. Extent of resection influences outcomes for patients with gliomas. Rev Neurol (Paris) 2011;167:648-54.
36. Barbosa BJ, Mariano ED, Batista CM, Marie SK, Teixeira MJ, Pereira CU, *et al.* Intraoperative assistive technologies and extent of resection in glioma surgery: a systematic review of prospective controlled studies. Neurosurg Rev 2015;38:217-26.
37. Talacchi A, Turazzi S, Locatelli F, Sala F, Beltramello A, Alessandrini F, *et al.* Surgical treatment of high-grade gliomas in motor areas. The impact of different supportive technologies: a 171-patient series. J Neurooncol 2010;100:417-26.
38. Eyüpoglu IY, Hore N, Savaskan NE, Grummich P, Roessler K, Buchfelder M, *et al.* Improving the extent of malignant glioma resection by dual intraoperative visualization approach. PLoS One 2012;7:e44885.
39. Feigl GC, Ritz R, Moraes M, Klein J, Ramina K, Gharabaghi A, *et al.* Resection of malignant brain tumors in eloquent cortical areas: a new multimodal approach combining 5-aminolevulinic acid and intraoperative monitoring. J Neurosurg 2010;113:352-57.
40. Ohue S, Kumon Y, Nagato S, Kohno S, Harada H, Nakagawa K, *et al.* Evaluation of intraoperative brain shift using an ultrasound-linked navigation system for brain tumor surgery. Neurol Med Chir (Tokyo) 2010;50:291-300.
41. Prada F, Del Bene M, Mattei L, Lodigiani L, DeBeni S, Kolev V, *et al.* Preoperative magnetic resonance and intraoperative ultrasound fusion imaging for real-time neuronavigation in brain tumor surgery. Ultraschall Med 2015;36:174-86.
42. Romanini L, Passamonti M, Aiani L, Cabassa P, Raieli G, Montermini I, *et al.* Economic assessment of contrast-enhanced ultrasonography for evaluation of focal liver lesions: a multicentre Italian experience. Eur Radiol 2007;17(Suppl 6):F99-106.
43. Firsching R, Klug N, Borner U, Sanker PR. Lesions of the sensorimotor region somatosensory evoked potentials and ultrasound guided surgery. Acta Neurochir (Wien) 1992;118:87-90

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Acknowledgements.—We would like to thank Ms. Tiffany Kristene Chimal for assistance in revising the manuscript.
Article first published online: March 11, 2016. - Manuscript accepted: March 9, 2016. - Manuscript revised: March 8, 2016. - Manuscript received: November 30, 2015.