Present day's standards in microsurgery of low-grade gliomas

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With 6 Figures and 2 Tables

Contents

Abstract

Low-grade gliomas are slow growing intrinsic lesions that induces a progressive functional reshaping of the brain. Surgical removal of these lesions requires the combined efforts of a multidisclipinary team of neurosurgeon, neuroradiolo-

gist, neuropsychologist, neurophysiologist, and neurooncologists that all together contribute in the definition of the location, extension, and extent of functional involvement that a specific lesion has induced in a particular patient. Each tumor has induced particular and specific changes of the functional network, that varies among patients. This requires that each treatment plan should be tailored to the tumor and to the patient. When this is reached, surgery should be accomplished according to functional and anatomical boundaries, and has to aim to the maximal resection with the maximal patient functional preservation. This can be reached at the time of the initial surgery, depending on the functional organization of the brain, or may require additional surgeries, eventually intermingled with adjuvant treatments. The use of so called brain mapping techniques extend surgical indications, improve extent of resection with greater oncological impact, minimization of morbidity and increase in quality of life. To achieve the goal of a satisfactory tumor resection associated with the full preservation of the patients abilities, a series of neuropsychological, neurophysiological, neuroradiological and intraoperative investigations have to be performed. In this chapter, we will describe the rationale, the indications and the modality for performing a safe and rewarding surgical removal of low-grade gliomas by using these techniques, as well as the functional and oncological results.

Keywords: Low-grade gliomas; brain mapping; fMRI; fiber tracking; neuropsychology.

Introduction

The term low-grade glioma refers to a series of primary brain tumors characterized by benign histology (low proliferation, low neo-angiogenesis phenomena) and aggressive behaviour related to the slowly progressive tendency to invade the normal brain parenchyma [22, 64, 80, 84, 107, 131]. These neoplasms are classified as grade II (out of IV) by the World Health Organization classification of brain tumors and include the following entities: grade II astrocytoma (further divided in fibrillary and protoplasmic), grade II oligoastrocytoma and grade II oligodendroglioma [72, 73]. Pilocytic astrocytomas, or grade I astrocytomas, are occasionally referred to as low-grade gliomas but due to their peculiar behaviour, require separate considerations. In this chapter, the term low-grade glioma will refer only to grade II tumors of the WHO classification.

Low-grade gliomas are slow growing tumors, typically affecting younger individuals (median age 35), mainly males (male/female ratio 1.5) which clinically present with seizures (often partial seizures) [83]. Headache, personality changes and focal neurological deficits represent the other most common symptoms. The neurological symptoms include motor/sensory deficits, dys-

phasia/aphasia, disinhibition, apathy, visuo-spatial disturbances and others according to the tumor location and size [22, 97, 110]. Interestingly, some authors reported the tendency of low-grade gliomas to occur in eloquent areas or in their proximity [40].

Overall, the median survival of low-grade gliomas is about 10 years and well defined negative prognosticators include older age (more than 40 years old), larger size (more than 5 cm), eloquent location and reduced Karnofsky performance status.

The optimal treatment for low-grade gliomas has yet to be determined. In fact, watchful observation, needle biopsy, open biopsy as well as surgical resection have all been advocated by different authors [10–12, 41, 44, 64, 81, 95, 106, 118, 135]. No evidence of class I, II or even III exists regarding the optimal management of these patients, even if the more modern tendency is to obtain at least some type of tissue diagnosis [67, 130]. Briefly, the rationale behind the observational or "wait and see" policy was the occasionally indolent or very slowly progressive behaviour of these tumors [81, 109, 135]. On the other hand, following the modern oncological concepts, some authors proposed to perform a biopsy in order to have a histopathological confirmation of the nature of the neoplasm before deciding the further management. Surgical resection of low-grade gliomas is still matter of debate but recent studies are increasingly supporting its role [10, 12, 26, 45, 67, 126, 130]. Surgery can in fact achieve multiple aims: first, it allows to obtain a more reliable histological diagnosis with eventually the molecular profile (e.g. 1p/19q loss and MGMT status); second, it permits to relieve symptoms; third, it has a beneficial effect on seizure control; in addition, surgery could decrease the rate of recurrence and of malignant transformation, as confirmed by recent studies [26, 45, 130]. Nevertheless, surgery carries its unavoidable risks, which even though low can potentially and permanently affect the patient quality of life.

Given this general information on low-grade gliomas behaviour and the possibility of treatment, it is clear that a modern surgical approach to low-grade gliomas has the goal to maximally resect the tumor mass, while at the same time minimizing the postoperative morbidity in order to preserve patient's functional integrity [12, 26, 45, 130]. In fact, since the natural history of the tumor can be relatively long (with or without surgery), the conservation of simple and complex neurological functions of the patients is mandatory. To achieve the goal of a satisfactory tumor resection associated with the full preservation of the patients abilities, a series of neuropsychological, neurophysiological, neuroradiological and intraoperative investigations have to be performed. In this chapter, we will describe the rationale, the indications and the modality for performing a safe and rewarding surgical removal of low-grade gliomas.

Rationale and indications

The major aims of surgical treatment are: 1) obtaining adequate specimens and representative tissue to reach a correct histological and molecular diagnosis; 2) achieving a cytoreduction in order to decrease the rate of recurrence and malignant transformation, possibly prolonging survival; 3) improving the neurological symptoms of the patients; 4) obtaining a better seizure control. These goals can be reached by tailoring the surgical approach on the peculiar features of location, modality of growth, and biological behaviour of low-grade gliomas.

Histological and Molecular Diagnosis: It is well known that astrocytomas or more in general primary brain tumors represent a challenge for the neuropathologist, mainly in the choice of the grading of the tumor. In fact, the specimens available are often not adequate in terms of size (e.g. needle biopsy) or not representative of the tumor to permit an accurate diagnosis. The size or the number of needle biopsy specimens does not always allow to perform all the eventually required immunohistochemical or molecular analysis, reducing the pathologist armamentarium for a correct diagnosis. In addition, the problem of the site of the biopsy can significantly change the final results because gliomas are typically very heterogenous and can have areas with different grades of malignity. Recently, the use proton MR spectroscopy of MR perfusion can partly overcome this last problem, giving informations on the presence of choline peaks (index of membranes production and malignancy) or areas of increased angiogenesis which can guide the surgeon in the decision of the best location for performing the biopsy [23, 50, 57]. In any case, the risk of underestimating, or more rarely overestimating, the grade is a concrete possibility for needle and even open biopsies eventually resulting in significant changes in the choice of the most appropriate treatment for the patients.

Molecular markers have become a standard for the determination of the type of low-grade glioma. In fact, chromosome 1p/19q loss of heterozygosity plays a very important role in the distinction between oligodendrogliomas and astrocytomas or oligoastrocytomas. The relevance of this molecular marker stays not only in the histotype definition but also in the different therapeutic implication [6, 24, 65, 129, 134]. In fact 1p/19q loss, as well as MGMT methylation (another important marker) resulted to be able to predict the response to certain chemotherapeutic agents [24, 48]. Obviously, inadequate or incorrect sampling of the tumor can dramatically impair the possibility of a molecular analysis.

Cytoreduction, Size and Location: Most of low-grade gliomas are localized close or within the so called eloquent areas, such as the areas of the brain which control motor, language or visuospatial functions. In a recent series, as well as in the experience of our group, 82.6% of tumors were located within eloquent motor or language areas (27.3% of cases within the SMA, 25.0% in the insula,

18.9% in language centers, 6.0% in the primary somatosensory area, 4.5% in the primary motor area) [6, 40]. As for the modality of growth, these tumors are characterized by a prevalent diffusive pattern of growth [40, 86]. In fact, groups of tumor cells or single tumor cells diffuse away from the main tumor mass along vessels or short and long white matter tracts [80]. These features are responsible for the typical aspect of low-grade gliomas seen in MR images, which is characterized by a morphology strictly resembling that of white matter tracts along which the tumor grows and diffuses. In addition, despite their occasional apparently indolent behaviour, low-grade gliomas are characterized by a continuous growth, with periods of faster and lower rates of growth during the entire time of the natural history of the tumor [86]. Some authors pointed out that most of the lesions judged as stable, actually did show various degrees of growth, and that minor changes in the diameter (e.g. 1–2 mm) reflect a significant cellular growth in term of volume [86]. For sake of simplicity, the rate of growth of a tumor can be quantified by measuring the maximal diameter onto FLAIR MR images. Repetitive measurement on representative sections demonstrated that the tumor continuously grows and that the mean increase of the tumor diameter is around 4 mm/year. Furthermore, an increase in tumor diameter larger than 8 mm/year, even in the absence of contrast enhancement or modification of T2 or FLAIR images, is associated with a high tendency toward malignant transformation and aggressive biological behaviour [105]. These data stress the point that serial measurements of tumor volumes are an important tool to determine the biological behaviour of the tumor. At the same time, it is clear that tumor volume is an important prognostic factor, able to determine per se the biological behaviour of the tumor overtime. In fact, larger tumor volumes are more frequently associated with a higher risk of malignant transformation and shorter patient survival [130]. Obviously, tumor volume is associated with the risk of developing neurological symptoms, increase in the risk of seizures, and probability of impacting in the social and professional life of patients.

Neurological symptoms: The majority of patients who are diagnosed with low-grade gliomas usually come to medical attention because of sudden occurrence of seizures [97, 130]. These patients are generally intact at the gross neurological examination, but they frequently present more subtle symptoms affecting complex neurological functions (memory, language, character, visuo-spatial orientation, etc.) which require a specific testing by a neuropsychologist [17, 53, 54, 55, 114]. As will be detailed below, this type of testing is mandatory when considering surgery for this type of lesions because it allows to tailor the intraoperative testing to the patient and permits to finely assess the impact of surgery on the patients superior neurological functions [1, 2, 59, 75, 76, 133].

Those patients who present with frank neurological deficits (e.g. hemiparesis, ataxia, aphasia) are usually candidate to surgery because their symptoms

are related to direct mass effect of the tumor on the cortex or on the subcortical white matter tracts. In this case, tumor removal can significantly relieve symptoms depending on the degree of the preoperative impairment as well as on the degree of parenchymal disruption. Obviously, this category of patients carries higher surgical risks in terms of morbidity and mortality than that of neurologically intact patients. Nevertheless, in terms of surgery, the presence of mass effect is a straightforward indication for tumor resection since a waiting policy will quickly bring to further neurological deterioration and even death in a limited span of time.

Seizures: Large tumors and insular locations are usually associated with a higher risk of developing seizures, which are difficult to be controlled by antiepileptic drugs, requiring the administration of multiple medications [25, 60]. Despite poly-therapy, seizure control can still be very poor. In these latter cases, surgery becomes an appealing option to improve seizure control. In fact, it has been clearly shown that surgical resection of low-grade gliomas is associated with a marked improvement in terms of seizures occurrence. In other cases, patients might be severely disabled by the side effects of multiple anti-epileptic medications and again surgery can allow to decrease the drugs administration. It is matter of debate whether surgical resection of low-grade gliomas for seizure control should be performed in an epilepsy surgery setting (with surface and eventually deep electrodes recordings, with resection of all the foci) or in a purely oncologic setting (with neurophysiologic monitoring including electrocorticography, but no deep electrodes and no resection of normal brain foci).

As mentioned above, surgery for gliomas aims to maximally remove the tumor mass and at the same time to preserve patient's functional integrity. This policy applies to the resection of any glioma but more specifically to those located close or within eloquent areas. The concept of eloquence refers not only to those areas which are involved in motor, language or visuospatial functions but also, more widely, to any area affecting the well-being of the individual (e.g. memory, socio-affective behaviour, specific tasks performance, etc.). In all these cases, extensive resection and maximal functional integrity can still be achieved through the intraoperative use of brain mapping techniques [6, 11, 12, 14, 36, 41, 45, 130].

The brain mapping technique

Performing brain mapping requires a series of pre-operative evaluations and intra-operative facilities which involve different specialists. A complete neuropsychological evaluation is generally the first step of the process permitting to select the suitable patients and to individualize the intraoperative testing. Then, sophisticated imaging techniques including fMRI and DTI-FT (Diffuse Tensor Imaging, Fiber tracking techniques) give the opportunity to attentively plan the

surgical strategies. In addition, these images can be loaded into the neuronavigation system becoming thus available peri- and intraoperatively for orientation. Intraoperative MR can be used as well, if available. Finally and most importantly, a series of neurophysiological techniques are employed at the time of surgery to precisely guide the surgeon in the tumor removal. These include cortical and subcortical direct electrical stimulation (DES), motor evoked potentials (MEP), multichannel EMG, EEG and ECoG recordings. All these techniques will be detailed in the next paragraphs. For reasons of simplicity, the management protocol will be divided in three parts: pre-operative, peri-operative, and post-operative.

Pre-operative protocol

The pre-operative part includes the neuropsychological and neuroradiological evaluation, which complete the standard neurological exam. A neuroanesthesiological evaluation should be performed as well for the selection and preparation of the patients from this perspective.

Neuropsychology

Neuropsychological evaluation is composed of a large number of tests for the assessment of various neurological functions such as the cognitive, emotional, intelligence, and basic language functions. Such a broad spectrum evaluation provides information on how the tumor has impacted on the social, emotional and cognitive life of the patient, who is generally intact at the neurological exam. It is important that the testing is the largest possible because the tumor which grows along fiber tracts, may alter the connectivity between separate areas of the brain, resulting in the impairment of functions which might not be documented in case of a neuropsychological examination limited to the testing of those functions strictly related to the area of the brain in which the tumor has grown [6, 42, 45]. When this extensive testing is administered, some alterations in the aspects of the neuropsychological exams can be documented in more than 90% of the patients [6, 45]. These data represent the baseline toward which the effect of surgical and future treatment should be compared. Additionally, when the tumor involves language or visuospatial areas or pathways, a more extensive specific evaluation should be added. Other than better defining the preoperative status of the patients, the neuropsychological assessment allows to build up a series of tests, composed of various items, which will be used intraoperatively for the evaluation and the brain mapping of various functions, among which memory, language in its various components, and visuospatial orientation are some of the most important. For language evaluation, patients are submitted preoperatively to extensive language testing composed of a battery of tests aimed to evaluate oral language production and comprehension, together with repetition [6, 36, 43, 103].

Table 1. *Neuropsychological assessment before and after surgery for low-grade glioma (Milano battery)*

Language examination (BADA): This is a psycholinguistic battery, exploring the sublexical, lexical, and morphosyntactic aspects of language and includes nonword and word repetition, sentence and phrase repetition, phonological discrimination
+
Token Test (norms and adjusted score for age and education)
Verbal fluency on phonological and semantic cue (norms and adjusted score for age and education available)
Word comprehension (alternatives of the same semantic category) (48 stimuli)
Object picture naming [six semantic categories: living (animals, fruit, vegetables) and non living (cloth, vehicles, tools)] (48 stimuli)
Action Picture Naming (50 stimuli)
Auditory Sentence Comprehension (80 stimuli)
Famous Face Naming (100 stimuli: 50 famous faces and 50 unknown) (norms and adjusted score for age and education available)
Short term memory:
Digit span (norms and adjusted score for age and education available)
Digit span backward
Corsi span (norms and adjusted score for age and education)
Assessment of long term memory:
Rey-Osterrieth complex figure test – delayed recall (norms and adjusted score for age and education available)
Prose recall (norms and adjusted score for age and education available)
Rey 15-word list learning (norms and adjusted score for age and education available)
Assessment of executive function and attention:
Verbal fluency on phonological cue (norms and adjusted score for age and education available)
Wisconsin Card Sorting Test (norms and adjusted score for age and education available)
Visual search, Stroop test, Trail making Test (norms and adjusted scores for age and education available)
Weigl Test (norms and adjusted score for age and education available)
Gambling Task (in case of frontal lesions)
Apraxia:
Face apraxia test (norms and adjusted score for age and education available)
Ideomotor apraxia test (norms and adjusted score for age and education available)
Rey-Osterrieth complex figure test – Copy (norms and adjusted score for age and education available)
Assessment of visuo-spatial abilities:
battery of tests like: letter cancellation, line cancellation, star cancellation, line bisection, sentence reading and copying task

(*continued*)

Table 1. (*continued*)

Line bisection (10 cm–15 cm–25 cm) (norms and adjusted score for age and education available)
Albert Test (norms and adjusted score for age and education available)
Diller Test (norms and adjusted score for age and education available)
Star Cancellation Test (norms and adjusted score for age and education available)
Copying Task
Sentence reading
Clock Drawing Test

Hemispheric language dominance is evaluated through the Edinburgh Inventory Questionnaire and fMRI. The following tasks are usually performed: Spontaneous speech; Oral controlled Association by Phonemic Cue; Famous face naming; Object Picture Naming; Action Picture Naming; Word Comprehension; Sentence Comprehension; Transcoding tasks. In addition the Token Test, the digit span, and counting are also performed. Ideomotor apraxia and face apraxia are also assessed. The majority of the tests generally used have been standardized on the normal population. In addition, different tests aimed to study the previous aspects of language can be found and adjusted according to the nationality of the patient. Generally, some tests as the BADA are available in different languages, others have to be normalized to the population. The list of the tests generally used in our center is reported in Table 1. It is important to include in the battery both qualitative and quantitative tests, and normative data must be available for the quantitative procedure. It is also important that a Speech therapist and a (neuro-)psychologist are managing the patients assessments. As mentioned above, preoperative language evaluation is also used to build up a series of tests, composed of various items, which will be used intraoperatively for the assessment of language during surgery. Among these tests, the object naming is probably the most important. In case of tumor located in dominant or parietal areas, number recognition and reading, as well as calculation or writing should be added in the preoperative testing and considered for the intraoperative evaluation [35, 51, 121]. When the patient is bilingual or is speaking more than two languages, it is important to include a large evaluation of the various languages in the preoperative testing [5, 52, 85, 120, 123]. Accordingly, the patient can be defined as early or late bi- or multi-lingual, depending on the time at which he or she has learned the various languages. In any case, a multi-lingual assessment is generally recommended.

Visuospatial functions are usually evaluated for tumor located in the parietal lobe, generally on the right side [45]. Unilateral spatial neglect is a complex and disabling syndrome that tipically results from right hemisphere damage, and it is characterized by an impairment of awareness of contralesional left half

of space, objects and mental images. In this case, the patient is presented with various tests such as the line bisection test or the star cancellation test to evaluate his or her spatial awareness (Table 1).

Imaging and neuroradiology

The neuroradiological examination is composed of basic exams, such as morphological T1, T2, and FLAIR images, as well as post contrast T1 images. These images together with volumetric sequences provide information on the site and location of the tumor, and allow to determine its relationship with various structures, such as major vessels, and to measure tumor volume. Further MR studies include MR spectroscopy, which provides information on the metabolic characteristics of the tumor, and allows to design a map of areas within the tumor in which tumor metabolism is more or less pronounced (multi-pixel MR spectroscopy map) [50, 57]. This is of great help in the tissue sampling at the time of surgery for histological and molecular purposes. In addition, perfusion MR studies are useful for designing perfusion maps, or maps in which the blood flow is depicted in the different tumor areas [8, 32, 79, 92, 93]. Being the regional blood flow dependent on tumor angiogenesis, these maps provide additional and complementary information of the biological behavior of the tumor and help in the tissue collection for histological and molecular purposes at the time of surgery [23]. Metabolic information may be also obtained by performing SPECT or PET, and these data may be incorporated into the navigation system for surgical guidance as well.

The neuroradiological investigations include functional studies, such as fMRI, and anatomic studies such as DTI-FT. The former provides functional information on the location of cortical sites which activates in response to motor tasks, or various language tasks [15]. Motor fMRI is generally used to design a map of the cortical motor sites and to establish their relationship with the tumor [62]. fMRI for language provides a map of the cortical sites which activate during various language tasks, such as denomination (object naming), verb generation, verbal fluency [121, 124]. All these data are put together to form a complex map of how the various components of language are organized at the cortical level and allow to establish the spatial relationship between these cortical areas of language activation and the tumor mass. It is usually recommended that language fMRI is performed with the same tests that are used for language evaluation in order to increase its reliability.

DTI-FT techniques allows to depict the connectivity around and inside a tumor, by reconstructing and visualizing the fiber tracts which run around or inside the tumor mass [4, 21]. DTI FT provides anatomical information on the location of motor tracts, mainly the corticospinal tract and various language tracts [7, 13, 27, 56, 63]. For a better visualization of tracts in low-grade gliomas, a FA (Fraction of Anisotropy) of 0.1 should be used, and additional

ROI for particular tract such as the anterior part of the superior longitudinalis or the SMA portion of the CST can be added [7]. The basic DTI FT map includes the CST for the motor part, and the such as the superior longitudinalis (SLF) which includes the fasciculus arcuatus, and the inferior fronto-occipital (IFO) tract for the language part [7, 36, 43]. The SLF is the basic tract involved in the phonologic component of language, the IFO is the basic tract involved in the semantic component of language. Additional tracts that can be reconstructed are the uncinatus (UNC) and the inferior longitudinalis (ILF) tracts, which provide information on the semantic and phonologic component of language in the frontal and temporal lobe, or the subcallosum fasciculus, involved in the phonologic component of language, sited in the lateral border of the lateral ventricle. Generally, preoperative DTI FT show that in low-grade gliomas most of the tracts involved either in language or motor function, are located within the tumor mass, and infiltrated or interrupted by the tumor. Although DTI FT maps are only anatomical and do not provide any functional information, DTI FT map can be used to predict resectability of a tumor. Globally considered, preoperative neuroimaging produces an impressive amount of information concerning the anatomical and functional boundaries of the lesion to be resected. Together with the volumetric morphological images, the DTI-FT images are usually loaded into the neuronavigation system, and help in the perioperative period in performing the resection. However, the imaging gives information based on probabilistic measurements, and although they may have a relatively high sensitivity or specificity, they still carry a certain amount of mistake which cannot, at least nowadays, be considered as sufficient for performing a safe and effective resection. This is the reason why the neuroradiological information loaded into the neuronavigation system has to be always supported during surgery by the results of the brain mapping. In other words, only the intraoperative brain mapping by means of electrical stimulation allows the surgeon to identify functional regions, that may be displaced and infiltrated by the tumor both at a cortical and a subcortical level, and thus to define the strategy of resection in order to maximize the extent of tumor removal while reducing the risks of permanent neurological deficits.

Anesthesiology

Besides the standard anesthesiological work up, the patient should be examined for his or her ability to be submitted to intraoperative awake monitoring when needed. A preparation and selection of the patients by anesthesiologists with expertise in awake surgery is recommended [29, 30]. In our Institution, the only absolute contraindication to awake surgery are the lack of cooperation, patients older than 65 years, or carrying obesity, those with difficult airways or affected by severe cardiovascular or respiratory diseases.

Intraoperative protocol

General policy of the surgical treatment is to remove the maximal amount of tumor and to preserve the functional integrity of the patient. This can be done by removing the tumor according to anatomical and functional boundaries. The anatomical boundaries can be defined by using neuronavigation or intraoperative MR; the functional boundaries can be defined by using neurophysiological, and neuropsychological adjuncts. The intraoperative protocol includes: anesthesia modalities; neurophysiology; neuropsychology; intraoperative imaging (neuronavigation and intraoperative MR).

Anesthesia

The patient can be maintained either awake for the full time of surgery, or awakened for the phase of the surgery during which the mapping is performed [5–7, 29, 30, 35, 36, 46, 127, 130]. Total intravenous anesthesia with propofol and remifentanil is used in our Institution for performing these procedures. In patients requiring only motor mapping, the patient is intubated through the nose and a light surgical anesthesia is maintained throughout the procedure. No muscle relaxants are employed during surgery to allow the neurophysiological assessment. When the language or the visuospatial functions have to be tested during surgery, the patients receive a laryngeal mask, which is maintained till after the craniotomy and dural opening [49]. At this point, the patients are awakened, while adequate analgesia is maintained, to allow functional monitoring. Time for awakening varies between 20 and 50 min, depending on the ability of the patient to metabolize the anesthetics. The anesthesiologist should be able to keep the patient awake for the entire time of subcortical mapping, which may require particularly during long lasting operations, to alternate period of resting with those during which the patient is fully awake and responsive. Patients fatigue is observed in most of the patients, and its appearance correlates with the duration of the mapping, and the difficulties of the testing (extensive language and visuospatial mapping) [5, 47, 50, 137]. Five percent of patients require the suspension of the mapping for a period longer than 20 min. The occurrence of seizures is the most important complication during the awake time of surgery, and can be controlled either by cold saline irrigation or by the infusion of a small bolus (1 ml) of propofol. Vomiting is a rare complication, and can be controlled by the administration of anti-emetics at the beginning of the phase of mapping [88].

Neurophysiology

The major components of the neurophysiological protocol are EEG, ECoG, EMG, DES and MEP techniques. The protocol includes mapping and monitoring procedures [9, 11, 16, 19, 28, 114, 117, 138].

In our Institution, EEG activity is recorded bilaterally by four subdermal needle electrodes, providing four bipolar leads. EEG is registered to monitor brain activity when EcoG is not available, i.e. at the beginning and the end of surgery, and, moreover, to assess brain activity at distance from the operating field, such as the contralateral hemisphere.

EcoG activity from a cortical region adjacent the area being stimulated is recorded by subdural strip electrodes with four to eight contacts, in a monopolar array, referred to a midfrontal electrode. Cerebral activity was recorded with a bandpass 1.6–320 Hz, and displayed with a sensitivity of 50–100 micron/cm for EEG and 200–400 micron/cm for EcoG. Continuous electrocorticographic recordings (Comet, Grass) are used during the entire duration of the procedure, to monitor the brain basal electrical activity, to define the working current (as that immediately below the one which induced an afterdischarge), to monitor for the occurrence of afterdischarges or electrical seizures during the resection.

A continuous multichannel EMG recordings (Comet, Grass) is used throughout the entire duration of the procedure. Several separate muscles belongings to agonist or antagonist muscles are monitored, either in the contralateral or ipsilateral body. Motor responses are collected by pairs of subdermal hooked needle electrodes inserted into contralateral muscles from face to foot. Each pair of electrodes records two different muscles in the same body segment, in order to sample as many muscles as possible (i.e. a flexor and an extensor muscle in the forearm). A number of 16 channels are used on average for each procedure. The most used setting is comprehensive of face (upper and lower face), neck, arm, forearm, hand, upper leg, lower leg. A computerized video and image capturing system is continuously coupled with the EMG recordings (Comet, Grass), to further monitor and register the motor activity. In addition to EMG recordings, motor activity is also evaluated clinically.

Direct electrical stimulation (DES) for cortical and subcortical mapping is performed by the use of a bipolar hand-held stimulator with 1-mm electrode delivered stimulation, according to Berger and coll., tips 5 mm apart, connected to Ojemann Cortical Stimulator (Integra Neuroscience) or a Osiris stimulator (Inomed, Germany), which is delivering biphasic square wave pulses, each phase lasting 1 ms, at 60 Hz in trains lasting 1 s for cortical mapping and 1–2 s for subcortical mapping. For subcortical mapping, either the same current used for cortical mapping or a current raised of 2 mA, is applied, and the stimulus is continuously alternated with resection.

For continuous monitoring of motor function, MEP recordings can be performed. The train of five technique, being introduced for surgery in anesthetized patients has been described as sensitive to detect imminent lesions of the motor cortex and the pyramidal pathways. A strip electrode containing 4 to 8 electrodes is placed over the precentral gyrus. In awake patients a single

stimulus or a double pulse stimulus (individual pulse width 0.3–0.5 ms, anodal constant current stimulation; interstimulus interval 4 ms, stimulation close to motor threshold) is usually delivered. The muscle motor evoked potentials (MEP) have to be recorded with either needle or – more convenient in awake patients- with surface EMG electrodes. MEP recordings is usually alternated with direct cortical motor mapping.

The purpose of the mapping procedure is to reliably test motor, language and cognitive function. For starting the mapping procedure, the initial activity is to define the stimulation parameters. As previously reported, a low frequency of 60 Hz is used, and the initial work is to establish the working current. As movement is easy to observe, it is advisable to start the procedure with mapping of motor function. Once determined the intensity of the current for stimulation, the same is used in most of the cases throughout the procedure, also for the mapping of cognitive and language functions. Initially, a low current intensity (2 mA) is used, and then progressively increased till a movement is induced. A stimulus duration of 1 or 2 s is usually enough to generate a motor response. At this point, it is good practice to stimulate the areas close to that in which the current induced the movement, in order to map them and to check if the current is able to evoke motor responses also in these zones. If not, the current intensity may be increased and adjusted in order to evoke appreciable motor responses. It is also recommended to check with the ECoG if the applied current may induce afterdischarges, in the nearby brain areas. In fact, only the current which is immediately below those which are inducing afterdischarges have to be used for mapping. If afterdischarges are seen, the current should be set up at least 0.5 mA under the previous one. In any case, ECoG recording is used to detect the appearance of afterdischarges during mapping, in order to keep the test reliable. In fact, only the responses evoked in absence of afterdischarges are considered to be trustworthy (Fig. 1).

For language mapping, the current which has evoked motor responses is tested. The initial test used is counting. The current is usually applied onto the face premotor cortex, and the test is aimed to check if the current is able to stop the patient to count. This has to be repeated several times and the counting to be stopped at least three times, in order to be reliable. If not, the current intensity is increased till this is produced. When the current is establish, the current is applied to whole brain surface exposed, and the occurrence of afterdischarges checked in the ECoG. The duration of the stimulus is between 3 to 4 s. Only the current which is not inducing afterdischarges in the entire brain surface to be mapped is used for mapping. In case of afterdischarges, the current intensity is decreased at least of 0.5 ms.

For cortical mapping, it is common practice to stimulate the whole of the exposed cortical area every 5 mm^2, to avoid the stimulation of the same cortical area twice consecutively. Each site have to be tested at least 3 non consecutive

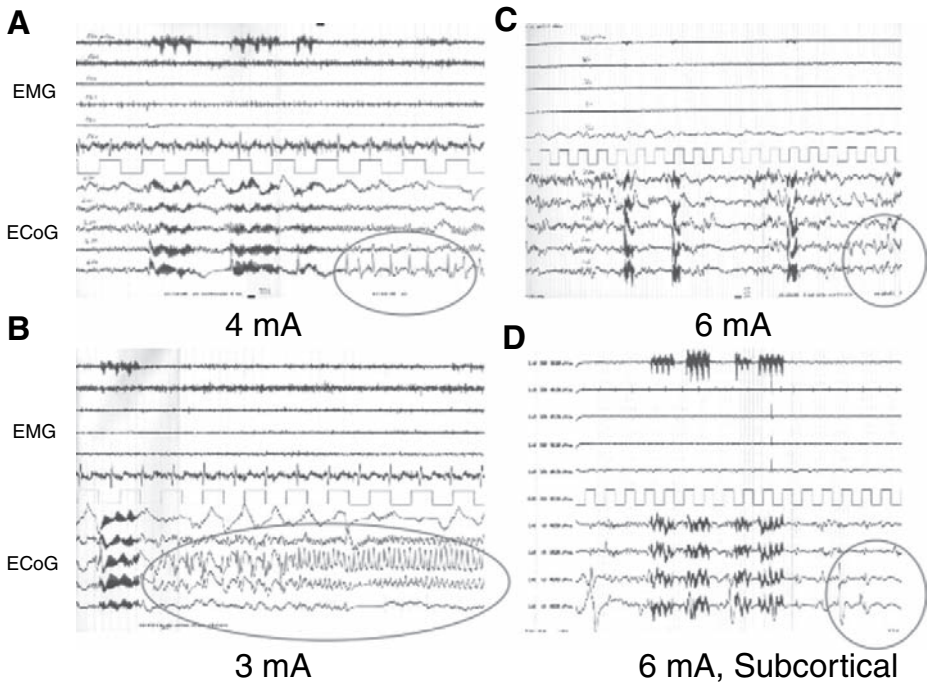
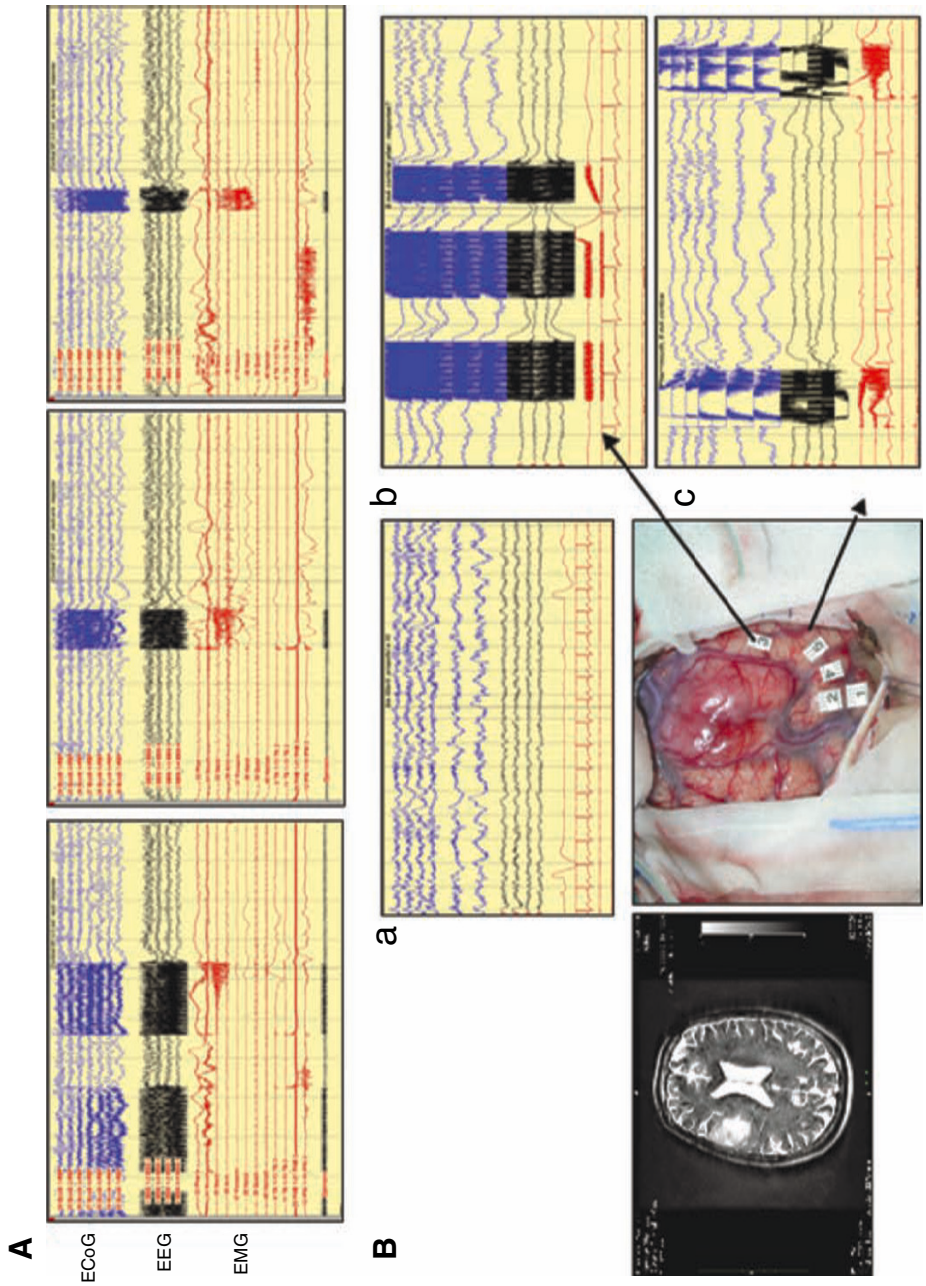


Fig. 1. ECoG monitoring during cortical and subcortical mapping. A, B) ECoG can be used to monitor the occurrence of afterdischarges. Afterdischarges (encircled) can appear as single or short train for spikes after the application of a stimulus. Intensity which can elicit the apperance of afterdischarges may vary according to the exitability of the cortex. C) Occasionally, spikes can organized and a electrical seizures may occur. EMG (upper lines) shows that no clinical activity was present. The electrical seizure was controlled by cold irrigation, D) rarely, single spikes may occur also during subcortical stimulation, when the stimulus is applied in the upper part of the pathways, not too far from the cortex

times before considering it either positive or negative. This is done to check the reproducibility of the responses, and to avoid the generation of responses due afterdischarges or electrical seizures.

It is important to keep the surfaces to be stimulated moist, not to stop mapping after identifying only one eloquent site, but to search for possible redundancies; a negative mapping does not protect, but creates the problem of questionable stimulation reliability. Stimulation intensity should be decrease during "control stimulations" in areas of "decompressed" brain tissues, in order to limit the risk of inducing a seizure. During deviation from optimal stimulation intensities, intra-operative electrocorticography can be very useful.

For subcortical motor mapping, the evoked responses are checked with EMG recording or clinically. For visuospatial subcortical mapping, the patient


A
ECoG
EEG
EMG
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a
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is presented with bisection or the cancellation test, for language subcortical mapping with a language test composed mainly of object naming or verb generation. Also during subcortical mapping ECoG is continuosly monitored to look for the occurrence of asfterdischarges and to assess for the occurrence of seizure and for the reliability of the responses (Fig. 1).

MEP monitoring is usually used the beginning of the procedure, and helps in identifying the location of the motor strip. During resection, MEP recording is alternated with subcortical motor mapping and provide additional information of the integrity of the motor pathways.

Results of the mapping or monitoring procedures

The previously described neurophysiological protocol has been applied on 400 consecutive patients submitted at our Institution during the last three years at surgical resection of gliomas located close or within motor, visuospatial or language areas or pathways. The majority of these cases were low-grade gliomas (79%), with a mean age of 37.6 years (ranging from 16 to 68 years).

Motor mapping

Motor responses were observed in all patients with lesions located close or within motor areas or pathways. We usually map motor responses in patients with tumors located in rolandic or premotor or parietal region. In addition, motor mapping is also applied at cortical and subcortical level for lesions located in the insula or deep temporal region, in which motor pathways can be encountered during resection. For lesions located in the non-dominant hemisphere, the patient is kept under general anesthesia, and the tube positioned through the nose. This allows the placement of a series of electrodes in the inner palate and pharyngeal muscles, as well as in the tongue, which are useful to detect responses from these muscles (Fig. 2). For lesions close or within visuospatial or language areas of pathways, the patient is always awak-

Fig. 2. Cortical motor mapping. A) The stimulus is applied over the area of the brain which is supposed to be the motor cortex. Stimulation of M1 induce quite sharp tonic responses; the stimulation of the motor cortex and allows to sequentially identify the areas of the brain which stimulation evokes movements of the mouth (upper and lower lips, left panel), of the hand (central panel) and of the forearm (right panel), allowing to define the progression of the motor homunculus. B) In patients under general anesthesia, electrodes can be place into the mouth, tongue, and pharyngeal muscles, allowing to identify the portion of the motor strip involved in these movements. Evoked responses are characterized by a EMG pattern (b) which is similar to that observed during spontaneous movements (such as swallowing), during the phase of discontinuation of anesthetics (a). The intraoperative picture shows the relationship between the tumor and the motor cortex. Arrows indicate the correspondence with the EMG responses. (c) indicates upper and lower lips evoked motor responses

ened during the procedure. In case of mapping performed under general anesthesia, the current intensity range between 5 and 15 mA, and the level of anesthesia which strongly influences the excitability of the cortex can be monitored by ECoG. In case of awake patients, a current intensity ranging between 2 and 8 mA is usually enough to evoke motor responses. In these patients, there are no electrodes placed in the mouth, and the activity of the muscles of this region can be checked by monitoring the responses of the patients and by overt inspection. Awake patients are asked to relax before and during stimulation, and to assist in the description of induced movements or in the sensory changes. A stimulation duration of 1 or 2 s is usually enough to generate a motor response. Cortical stimulation induces focal motor responses. EMG recording provided an excellent view of the whole contralateral body at the same time, reducing the risk to miss responses in segments difficult to inspect, due to the position of the patient on the operating table or to detect, such as the mouth or pharyinx (Fig. 2). We observed different morphologies of EMG responses: cortically evoked responses showed great variations in amplitude, but they appeared always as continuous, tonic bursts of activity, often incrementing during stimulation. Smallest amplitudes were observed in the neck and the shoulder, or in the mouth. Occasionally in patients under general anesthesia and receiving a large amount of anti epileptic medications, it might be difficult to evoke cortical motor responses, even after the current intensity has been increased till to that which might induce the appearance of afterdischarges. In these patients, the use of MEP recording can be useful for identify the location of the motor cortex and to plan the site of incision, allowing continuing resection. During subcortical stimulation, motor responses appeared as focal (few muscles) when the tract is stimulated in close vicinity to the surface, while they appeared on multiple muscle groups with deep stimulation. Subcortical stimulation evoked both tonic bursts and on-off activity, i.e. a M-shaped response, peaking at the onset and the end of stimulation. For resection of tumors located in premotor cortex, the placement of electrodes in the ipsilateral muscles allows to detect during resection responses coming from these segments. In addition, when resection is approaching deep portion of the tumor, subcortical stimulation it allows to detect small motor responses without overt muscle activity, which indicate that the resection is becaming close to motor pathways (Fig. 3). When these warning responses are identified, resection should became particularly careful in this region and can proceed till more pronounced motor responses are identified, usually when the tip probe is touching and stimulating the motor pathways. The identification of such pathways is therefore particularly useful for performing a sage and effective resection.

The simultaneous use of CUSA and DES at subcortical level in proximity of the cortico-spinal tract may bring to the abolition of previously evident motor responses. This abolition is generally fully reversible after turning the

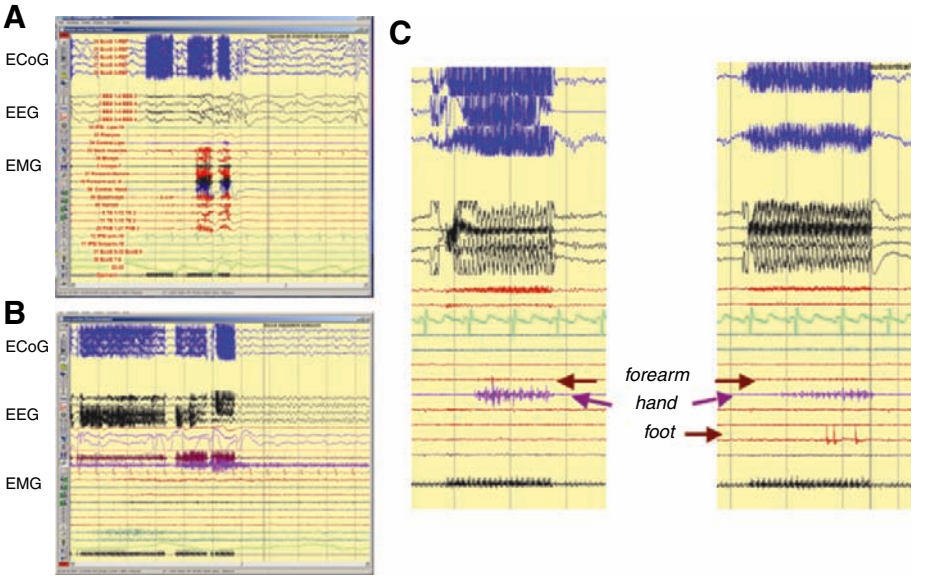


Fig. 3. Subcortical motor stimulation. A) EMG allows to monitor subcortical motor mapping responses. When the resection is approaching the internal capsule, the stimulation of the peripheral portion of the corticospinal tract induce evoked motor responses which involves all the segments of the body, from the upper to the lower arm (upper panel). B) The placement of electrodes in the pharyngeal muscles allows to identify the subcortical tracts which are involved in this function. C) The use of EMG allows to identify motor tracts before that overt motor responses are visible. This is particularly useful in the deeper part of the resection cavity, and reduce the risk of motor tract injury. The responses for the forearm, hand, and foot were not clinically visible and were induced for stimulation of deeper part of the resection cavity, close to the internal capsule

CUSA off. An analogous pattern of inhibition of motor responses can be also evident when the DES is applied cortically and CUSA used subcortically close to motor pathways. This interference with motor mapping may be interpreted as a transitory inhibition of axonal conduction. The clinical significance of this interference is relevant when CUSA and DES are used simultaneously for motor mapping because it can decrease the sensitivity of the brain mapping technique, and should be kept in mind by the surgeon when during resection is using both tools [20].

Motor monitoring

For continuous motor monitoring with MEP, a second EcoG strip electrode is placed over M1, delivering monopolar pulses to elicit Motor Evoked Potentials (MEP) in a few target muscles: MEP are monitored throughout the surgery,

except when the surgeon needs direct subcortical mapping for mapping purposes. MEP monitoring is very useful because it provides on line information of the integrity of the motor pathways during resection of large part of the tumor not closely located to functional structures. In addition, MEP provides warnings of impending brain ischemia, due to critical vessel interruption, mostly in deep temporal or insular regions [96].

Language and visuospatial monitoring

The current intensity generally applied for language mapping in awake patients is ranging between 2 and 9 mA. To identify malcompliance or impairment not related to stimulation e.g. a non-convulsive seizure, each stimulation should start before the presentation of the material started. Each stimulation should be followed by at least a task without stimulation, and two tasks are the standard. Being the duration of the stimulation longer than that for motor mapping (4 s vs. 1–2 s) repetitive stimulation might trigger afterdischarges or seizures.The stimulus is applied immediately before the item is presented to the patient, and a neuropsychologist who is present in the OR is evaluating the performance of the patient during the various tests administered at both cortical and subcortical level to maintain patient language integrity. Various type of mistakes can be encountered during the performance of the tests (Table 2). The mistakes can occasionally occur without stimulation, or more frequently during stimulation. It is important during the administration of each test to check the ECoG and EEG for the occurrence of afterdischarges or electrical seizures. Only the mistakes in the absence of ECoG disturbances are reliable. In addition, a site can be define as essential for language when it produces language disturbances at least three time in various non consecutive stimulation. Cortical language sites coding for object naming, verb generation, face naming, word or sentence comprehension, numbers or colors can be identified in several regions in the frontal, temporal or parietal lobe, which a distribution which differs according to patient and patient gender. For subcortical language mapping, the patient is asked to perform a object naming and a verb generation task during which the surgeon can continue to perform resection which is alternated with stimulaton.

Table 2. *List of the most common mistakes encountered during cortical and subcortical language mapping*

– Anomia, misnamimg or incorrect word insertion
– Phonemic paraphasia
– Semantic paraphasia
– Use of complex sentences
– Initiation disorders
– Latency of response
– Voice disturbances: sillabic modification, pseudo-accent, hypophonia

When a language disturbance is produced, the site is then carefully tested for the occurrence of semantic or phonemic paraphasia. Each tract is characterized by involvement in the semantic (inferior fronto occipital tract, uncinatus,. . .) or phonemic (superior longitudinalis, inferior longitudinalis, subcallosum) and can be recognized at a subcortical level by the appearance of semantic or phonemic paraphasia associated with typical language disturbances, such as for examples speech arrest for the subcallosum. Also during subcortical language mapping it is very important to check for the occurrence of afterdischarges or electrical seizures, in order to minitor the reliability of the testing. During subcortical mapping it is also possible to evoked motor responses, due to the identification and stimulation of motor fibers belonging either to the premotor component of the face which induce anarthya, or to the corticospinal tract, which induce various type of muscle activation depending on the location and deep of stimulation. Generally, this occurs in 20% of cases.

Visuospatial mapping is performing usually in patients with lesions located in the parietal lobe, and in case of dominant location it is intermingled with language mapping. The patient is usually requested to look at the appearance of a line in a touch screen and to bisect the line, by touching its center with a pen. A deviation toward right or left over 2 cm is usually considered as pathologic, and associated with an interference in the visuospatial function. The current intensity is the same as for cortical motor mapping. The same procedure is also performed at subcortical level by using the same current intensity or a current up to 2 mA over the previous one. Subcortical visuospatial mapping identified a small and discrete tract usually running al the lateral mid border of the tumor which is involved in this function. The preservation of this tract as well as of the cortical sites, prevents the occurrence of neglect during the post operative course. As for language and motor mapping, ECoG and EEG should be monitored during the entire duration of the test to check for its reliability.

EEG and ECoG monitoring

EEG and ECoG recordings should be kept during the entire duration of the procedure because it allows to monitor for the occurrence of afterdischarges, electrical seizures or even clinical seizures. Group of ECoG spikes or electrical seizures occur in up to 30–40% of cases, and can be or not related to stimulation. In any case, when they appear it is recommended to irrigate the cortex and the surgical cavity with cold saline, that result in the majority of the cases in the control and reversal of the situation. Clinical seizures occur in 8% of cases, and most of them are focal. The use of cold saline irrigation is able to control and totally revert most of them. In these cases, the EEG is useful to look for the cases of diffusion of the seizure, either at the same or even worse at the contralateral hemisphere. The few clinical seizures we observed appeared most frequently at the end of tumor resection, when cortical stimulation was applied

to assess the integrity of the motor pathway. The current was subsequently reduced, and no seizure was observed anymore. This stress the point that at the end of the surgical resection it might be requested to reduce the intensity current, due to the reduction of the mass effect exerted by the tumor mass of the surrounding functional parenchyma. In selected cases, ECoG can be used to detect generation of spikes in specific areas of the cortex, in close or not vicinity with the tumor mass, and that are responsible for sustaining electrical activity.

Intraoperative imaging

The neuronavigation system is loaded with morphologic volumetric T1 and T2 images, along with motor and language fMRI and DTI FT images. Neuronavigation helps during surgery to localize the tumor, and to define the relationship between the tumor and the surrounding functional and anatomic structures, both at cortical and subcortical level. As estimate for the clinical navigation accuracy, the target registration error localizing a separate fiducial, which is not used for registration, is usually performed at the beginning of surgery. The target registration error should be less than 2 mm. The main limitation of the use of a neuronavigation system, particularly in case of large tumors, is the occurrence of brain shift, which occurs already at the beginning of surgery, when the dura is opened, and increases with the progress of tumor removal [7, 66, 68, 101, 113, 125]. Resection should be performed in order to maintain the maximal accuracy of the neuronavigation system, to reduce the problem of brain shift: repeated landmark checks are performed during surgery to ensure overall ongoing clinical navigation accuracy; the use of a craniotomy limited to the minimum necessary to expose the tumor area and a limited portion of the surrounding brain, allows to minimize brain shift; in case of frontal tumors located in the proximity of CST, resection is started from the posterior border where the CST is located and, after its identification, the tract is followed inside the tumor mass. Afterwards the remaining anterior part of the tumor is removed. Similarly, in case of parietal tumors, resection is started from the anterior border following the same principle. The value of the localization of functional areas obtained from fMRI in tumors has been studied by correlating fMRI data with intraoperative cortical stimulation. For motor correlation, the results of the direct cortical stimulation matches those obtained with fMRI, both positively and negatively, although the extent of the functional activations was larger than the area defined with intraoperative mapping, and results are strictly dependent on the type of task used for testing [15, 82]. These data indicates that motor fMRI can be safely used for planning surgery. For the language correlation, the results are variable and different according to series. Naming and verb generation tasks are those which are most widely used for language fMRI studies. Generally, language fMRI data obtained with naming or

verb generation tasks were imperfectly correlated with intraoperative brain mapping results (sensitivity 59% and specificity 97% when the two fMRI are combined) [108, 121, 124, 136]. Generally, fMRI is showing larger activation than those observed with direct cortical mapping, which on the contrary, demonstrates only essential language sites. In our experience, the sensitivity can be increased up to 72% by using in the fMRI naming tasks the same figures used during surgery. Nevertheless, also in this condition, false negative can be documented in up to 8% of patients. Therefore, language fMRI could not be used to make critical decisions in absence of direct brain mapping. As for DTI FT, it is important to remember that DTI FT is providing anatomical information whereas subcortical mapping functional ones. This affects the correspondence and concordance between DTI FT images and functional

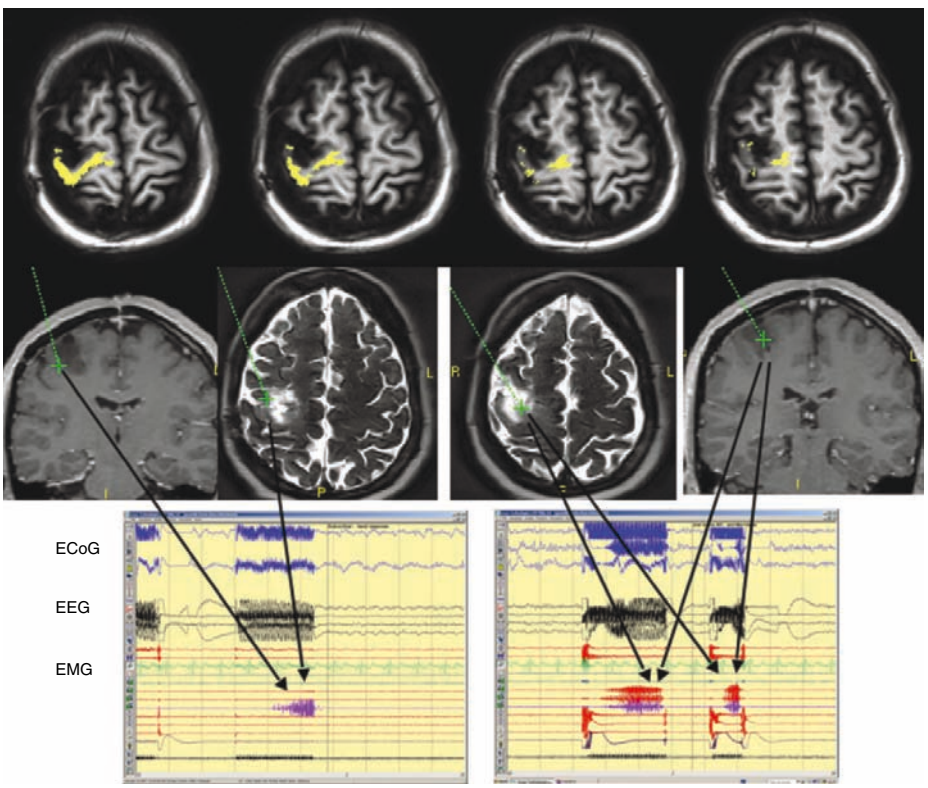
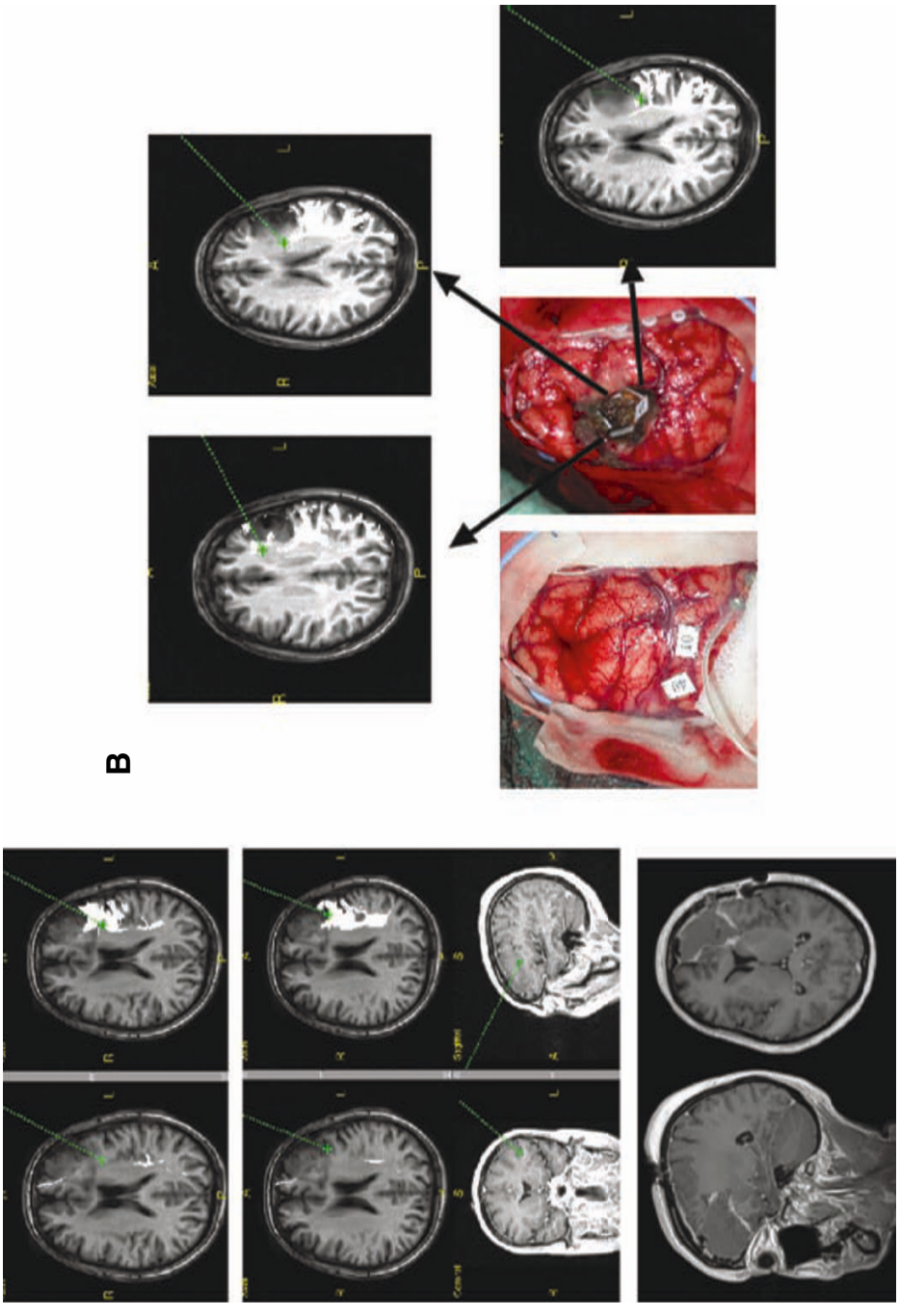


Fig. 4. DTI FT and subcortical motor mapping. When combined with subcortical mapping, DTI FT helps the surgeon in the safe identification of subcortical motor tracts, which like in this case of motor grade II oligodendrogliomas, were located at the peripheral portion of the tumor. Stimulation of these tracts elicited evoked motor responses for the hand (left lower panel) in the superior part of the resection cavity, the hand, lower and upper lips (right lower panel) when the resection was approaching the deeper part of the tumor

information obtained with subcortical mapping [7, 13]. This is of relative importance for CST (Fig. 4), but of particular relevance for language tracts, in which the anatomical distribution of the tract as depicted by DTI is larger than the functional ones obtained with mapping. Therefore, large part of the tract as depicted by DTI FT can be removed because not functional for the function tested at that time. When a FA of 0.1 is used for tracking, there is usually a good concordance between DTI FT data and subcortical motor mapping (sensitivity for CST = 95%, language tracts = 97%). Some pitfalls may occur for low-grade gliomas located in rolandic or SMA areas. DTI FT may fail in reconstructing portion of CST, particularly in area of extensive tumor infiltration. Even the placement of additional ROI at this level only partially improves reconstruction. As for SLF, the anatomic distribution of this tract is usually quite larger than the functional ones when language subcortical mapping is performed (Fig. 5). This is particular the case of frontal and temporal tumors. In low-grade gliomas, SLF is often depicted inside the tumor mass. As for the IFO, the anatomic distribution of this tract is small and usually corresponds to the functional one depicted by subcortical mapping (Fig. 6). Some problems may occur for F3 low-grade gliomas in which DTI FT may fail in reconstructing the more superior part of the tract at the inferior border of the tumor, when the tumor infiltration in this area is quite extensive. As for the UNC, the anatomic distribution of this tract is small and usually corresponds to the functional one depicted by subcortical mapping. The reconstruction of this tract in F3 tumors requires the placement of an additional ROI at this level. In F3 low-grade gliomas, the tract is usually inside the tumor mass, and the

Fig. 5. DTI FT and subcortical language mapping. DTI FT for SLF were fused with T1 weighted MR images and loaded into the neuronavigation system. A) The DTI FT reconstruction of the SLF is larger than the functional ones identify by subcortical language mapping and the non functional portion of the tract visualized by DTI FT can be safely removed. The upper panel is showing an intraoperative snapshots from the neuronavigation system which indicates the location of a subcortical sites where phonemic paraphasias were evoked. The portion of the SLF place anteriorly to this point was safely removed because not functional. The mid panel is showing showing an intraoperative snapshots from the neuronavigation system which indicates the location of a subcortical sites where phonemic paraphasias were evoked, demonstrating in this case a good correlation between DTI FT reconstruction and subcortical language mapping data. The lower panel is showing post operative post contrast T1 weighted MR images. B) A case of left frontal F3 grade II oligodendroglioma, in which SLF constitutes the anterior, upper medial and upper posterior border of the resection cavity. Arrows indicate the correlation between intraoperative snapshots and subcortical sites at the border of the resection cavity. The lower left picture shows the results of the cortical motor and language mapping. The tags indicate areas of the cortex in which stimulation induced speech disturbances


B
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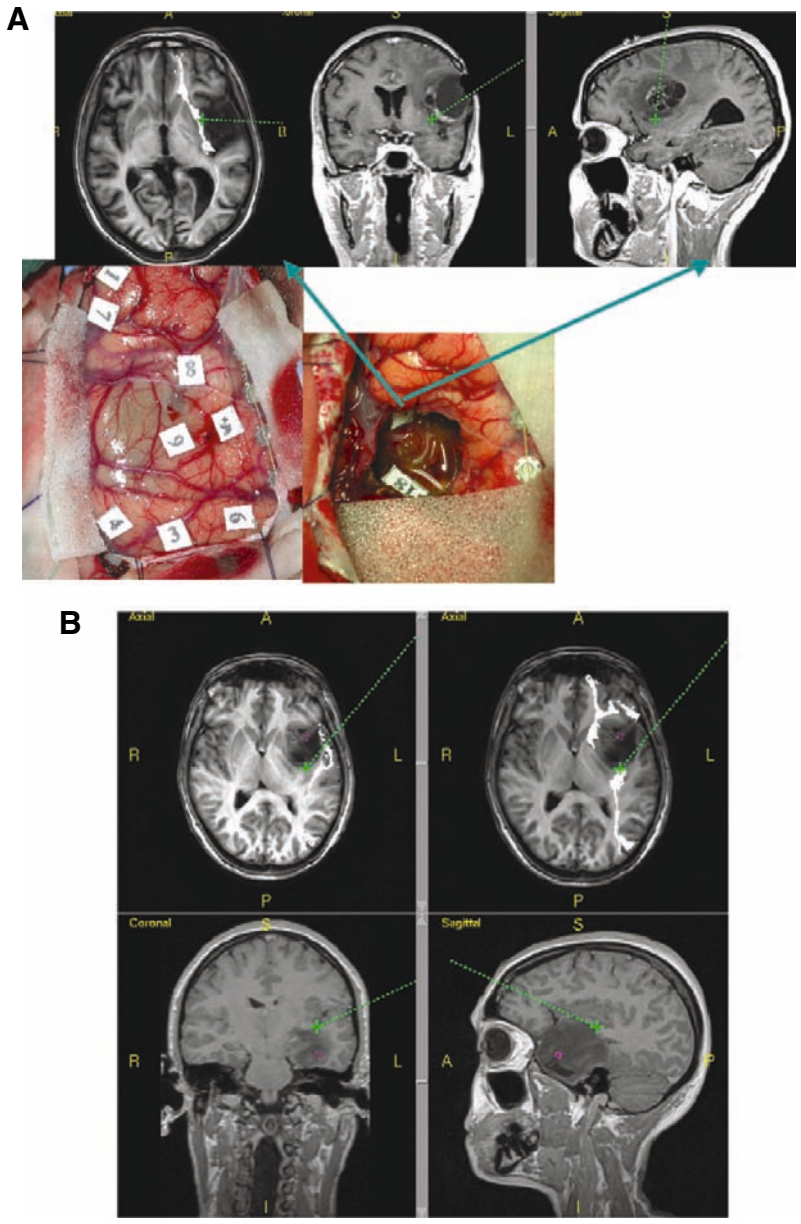

Fig. 6. DTI FT and subcortical language mapping. DTI FT for IFO were fused with T1 weighted MR images and loaded into the neuronavigation system. The IFO is small discrete tract, and when encountered is always functional. A, B) Examples of good correlation between DTI FT reconstruction for IFO and suncortical language mapping. In A) the IFO constitutes the medial inferior margin of the resection cavity of a cystic recurrent grade II oligodedroglioma. In B) the upper medial margin of a left temporal grade II oligodendroglioma

depicted fibers are usually found as functional by subcortical mapping. In temporal LGG tumors, the tract is still described as inside the tumor mass, but the fibers are extensively infiltrated and interrupted, and not functional.

Intraoperative MR has been more widely used for surgical treatment of low-grade gliomas [26, 69, 90, 98, 100]. Surgery for low-grade gliomas has been performed by using both low (0.2 or 0.5) or high (1.5) magnetic fields. The advantage of using intraoperative MR images is to have a precise jugdement of surgical removal while the patient is still in the operating room. In addition, by performing repeated images during surgery, it is possible to update morphological images and by transferring them into the neuronavigation system, to overcome the problem of brain shift [132]. Progression of surgery can be followed, and the occurrence of intraoperative complications monitored [91]. Furthermore, associated MRI software allows for a more precise estimation of initial and resected MRI tumor volume, permitting an improved measurement of the exposure variable. Usually in at least in 20% of cases of low-grade gliomas, a remnants of the tumor can be visualized in the field, and further removed [94]. The main limit of the intraoperative MR system is the cost of the machine and of the instrumentarium. The use of low field may permit the use of nonmagnetic surgical instruments, and are characterized by a lower cost of installation and of the machine. Varies low field machine are available, either the 0.2 Polestar or the 0.5 GE machine. The 0.5 GE prototip allows on time intraoperative images during surgery, but is limited by the restricted surgical room and by the need of using a complete nonmagnetic surgical tools. In addition, low magnetic fields do not permit to perform fMRI or DTI FT studies. Intraoperative high-field magnetic resonance (MR) system is at present one of the most sophisticated technical methods providing a reliable immediate intraoperative quality control. It enables intraoperative imaging at high quality that is up to the standard of up to date pre- and postoperative neuroradiological routine diagnostics. High-field MR imaging offers various modalities beyond standard anatomical imaging, such as MR spectroscopy, diffusion tensor imaging, and functional MR imaging which may also be applied intraoperatively, providing not only data on the extent of resection and localization of tumor remnants but also on metabolic changes, tumor invasion, and localization of functional eloquent cortical and deep-seated brain areas. Various systems have been developed and variable used. In most of them the patient is located into a bed and moved with into the magnet for MR images. Recently 3T MR systems have been put in place, or are under construction, like in our Institution. Both fMRI and DTI FT have been demonstrated to be feasible in these systems. Nevertheless, fMRI requires the patients to be awake and perform tasks inside the scanner. In addition, the quality of the generated data is often not as good as what can be achieved pre operatively. Furthermore, the time needed to acquire and process the data is often substantial. An alternative

approach used in recent device is therefore to acquire fMRI and DTI FT pre operatively, and track the anatomical changes that occur during surgery using intraoperative MR images and apply the changes found to the pre operative data [3, 99, 100, 102].

Ultrasound is another imaging option used for intraoperative visualization of low-grade gliomas. Advances in ultrasound technology have made the image quality of the ultrasound comparable to intraoperative MR [112]. Recent studies showed that the integration of intraoperative ultrasound with neuronavigation represents an efficient and inexpensive tool for intraoperative imaging and surgical guidance. Brain shift detected with intraoperative ultrasound could be used to update pre operative image data such as fMRI and DTI FT in order to increase the value of this information thorought the operation. The ability of these methods to reveal forgot tumor remnants is lower than that of intraoperative MR systems.

Immediate post operative course

When resection is perfomed according to functional boundaries, this is associated with a high incidence of development of immediate post operative deficits (over 70%), due to the functional blockage of the system (see the following paragraph). During this period patients are submitted to neuropsychological evaluation, motor rehabilitation, to follow deficit recovery, and to standard post operative imaging, including T1, T2 and flair volumetric sequences, to evaluate extent of resection.

Functional results of surgery

When brain mapping techniques are applied to low-grade glioma surgery, functional results can be evaluated either at early (within one week) to late (from one month to three months) time after surgery. The purpose of brain mapping techniques is to identify and preserve at the time of surgery cortical and subcortical essential sites. Resection was in fact stopped when language and/or motor, or visuospatial, cortical or subcortical areas were encountered. In most of in low-grade gliomas, motor or language disturbances were evocated either inside the tumor mass as well as at the tumor margins, because most of the essential sites particularly at the subcortical level are located within the tumor. The preservation of subcortical tracts is therefore critical for patient integrity [6, 7, 12, 36, 41, 43]. Evaluation of motor or language deficits during post operative course and at follow-up, showed that the chance to develop a new deficit or to worsen a preexisting one in the immediate post operative period was 72.8% and 65.4% in the group of patients in which language or motor related areas were identified subcortically during resection, and very low in the

group of patients in which no subcortical sites were identified [6, 70]. The chance was also higher in patients with a pre-existing motor or language deficit, which correlates with the higher percentage of subcortical tracts identified in the same patients. Most of the deficits were transient and disappeared within one month from surgery. Nevertheless, in the group of patients in which a subcortical language site was identified during resection, the likelihood to develop a permanent deficit was 3.8% independently from histology and location, that reached 7% in patients with a pre-existing motor or language deficit. In contrast, when no subcortical sites were found at the time of surgery, the chance to induce permanent deficit was very low (2%). This percentage further reinforce the concept that when a subcortical site is found, the surgeon is very close to the subcortical pathway. Therefore, when a subcortical response is reliably detected, resection must stop and should be continued in the neighborhood structures, because there is a high chance to damage functional structures [6, 43, 70]. If no subcortical structures are found, the resection can be continued, because the chance to hamper essential structures is low. These data indicate subcortical stimulation as a reliable tool able to guide surgical resection, and at the same time to predict the likelihood to develop deficit post operatively. The low incidence of post operative deficits in patients in which no subcortical tracts were identified is usually due to vascular damage and at the development of ischemic areas. MEP monitoring can help in monitor and preventing the appearance of motor deficits due to vascular injury [96]. When subcortical stimulation was systematically applied during resection of low-grade gliomas located within language areas or pathways, 79.5% of patients had a long term post operative normal language, 18.6% showed mild disturbances still compatible with a daily life useful language, and only 2.3% showed a long term impairment. Similar figures were observed for resection of gliomas close to motor areas or pathways. These functional results were totally different from those obtained when subcortical stimulation was not applied. Analysis of patients with high- or low-grade gliomas operated on in our Institution before the use of direct electrical stimulation, showed 23% of permanent language or motor deficits, in accordance with what has been previously reported in other series [6, 33, 41]. These data support the relevance of subcortical stimulation as a useful surgical adjunct during removal of lesions involving motor or speech areas, as further demonstrated by the high percentage of patients (91.8%) who returned to work at three months after surgery.

Oncological results of surgery

From an oncological point of view surgery, wishes to different aims: precise histological and molecular diagnosis, relief symptoms, reduce the incidence of

seizures, reduce the rate of recurrence and of malignant transformation, and possibly increase patient survival.

The ability of surgery to allow the pathologist to reach a more precise histological diagnosis and to relief symptoms particularly in case of large tumors inducing a mass effect, is at now less a matter of debate, although simple biopsy without resection, will continue to be theoretically acceptable and will continue to be practiced until better evidence is available.

The effect of surgery on the incidente of seizures has been recently documented by several authors [16, 43]. Seizures play an important role in the clinical presentation and postoperative quality of life of patients who undergo surgical resection of low-grade gliomas [74]. At least 50% of patients have a seizure at diagnosis and in more than 81% seizures persist after diagnosis even when the patient are under anti epileptic drugs (AED) treatment. Cortical location and oligodendroglioma and oligoastrocytoma subtypes are significantly more likely to be associated with seizures compared with deeper midline locations and astrocytoma. Forty-nine percent of patients have pharmacoresistant seizures before surgery. A particolar case is that of insular or paralimbic tumors. In these cases, intractable epilepsy is observed in 30% to 58% of cases and patients may experience up to 10 partial seizures per day despite more than 2 AEDs. Seizure control is more likely to be achieved after gross-total resection than after subtotal resection/biopsy alone. In fact when total or subtotal resection is achieved, in a more than 80% of cases a positive impact on seizures is documented, with reduction in the number of AED administered. In addition, suppression of AEDs is possible in 30% of cases [43]. Also in more than 80% of cases of insular low-grade gliomas with intractable epilepsy, a positive impact on seizures can be again documented. It is of relevance to remember than in low-grade glioma patient in which a seizure control has been reached after initial surgery, seizure recurrence is associated with tumor progression [16].

The first oncological result of when surgery is performed according to brain mapping techniques, is the increase in the number of cases who are submitted to surgical treatment, that in accordance of what has been previously reported in the literature, in our series moved from 11% of cases when mapping was not available, to 81% when mapping was applied, with a significant decrease in the number of cases that were submitted to biopsy only [6, 33, 41]. The second oncologic result, already discussed in the previous paragraph, is the decrease in the percentage of post operative permanent deficits, that felt from 33% to 2.3%, either for language or motor functions [6, 41, 43, 130]. The influence of extent of resection on time to recurrence, time to malignant transformation, and patient survival, is still a matter of debate. Nevertheless, a large number of class III and II evidences suggests that more extensive resection at the time of initial diagnosis may be a favorable prognostic factor for this type of tumors [10, 12, 18, 26, 41, 67, 89, 118, 126, 130]. The evalua-

tion of extent of resection is usually performed on post operative FLAIR volumetric images, by the aid of semi automatic segmentation software [71, 87]. The ability to achieve a complete resection (no abnormalities seen on post op FLAIR images) or subtotal resection (a post operative volume on volumetric post op FLAIR images less than 10 ml) is influenced by both the pre operative tumor volume and by tumor involvement of eloquent tissue, particularly at the subcortical level [130]. Pre operative tumor volume is a significant predictor of patient survival and progress free survival per se, as well as the involvement of subcortical tracts. Patients with tumors larger than 50 ml has a much shorter overall survival and progression free survival than those with tumors smaller than 25 ml. When the effect exerted by these two variables is analyzed together, the intraoperative finding of subcortical tracts is the parameter which mainly influences the ability to perform a complete removal, independently from tumor volume [6]. In a recent work [130], Berger showed that, after adjusting for the effects of age, KPS, tumor location, and tumor subtype, postoperative tumor volume remained a significant predictor of overall survival and progression free survival. Patients with a complete resection of FLAIR images have a significantly longer over all survival compared with patients having any residual FLAIR abnormality. In the same work, Berger and collegues subdivided patients with subtotal resection, in two subgroups, on the basis of postoperative tumor volume to specifically address the risk of relatively small volumes of residual tumor. Patients with residual FLAIR abnormality volume between 0.1 and 5.0 or between 5.1 and 15.0 ml demonstrated significantly shorter overall survival compared with patients who had complete resection of FLAIR abnormality. In addition, lower was the post operative volume, longer was the overall survival. Similarly, progression free survival was influenced by the post operative tumor volume. In our series of primary low-grade gliomas, no recurrence were observed at 5 year when the tumor was complete removed (no FLAIR abnormalities), whereas the percentage of recurrence at 5 year was 16.7% in case of subtotal removal (residual tumor volume less than 10 ml) and 38.5% in case of partial removal (residual tumor volume higher than 10 ml). In Berger analysis, after adjusting for the effects of age, KPS, tumor location and tumor subtype, extent of resection remained a significant predictor of overall survival and of time to malignant transformation. In our series, time to malignant transformation was 3.8 years in case of partial surgery, and 7.8 years in case of subtotal removal. Patients with at least 90% removal had 5- and 8-year overall survival (OS), progression free survival (PFS), and malignant progression free survival (MPFS) rates of 97% and 91%, 75% and 43%, and 93% and 76%, respectively, whereas patients with less than 90% removal had 5- and 8-year OS, PFS, and MPFS rates of 76% and 60%, 40% and 21%, and 72% and 48%, respectively. Patients with complete resection of all FLAIR abnormality had 5- and 8-year OS, PFS, and MPFS

rates of 98% and 98%, 78% and 48%, and 96% and 79%, respectively. When multivariate analysis was used, extent of resection was predictive of overall survival, whereas preoperative volume of progression free survival and time to malignant transformation [10, 130]. Globally considered, these data stress the importance of extent of resection in controlling tumor growth and influencing survival. Pre operative tumor volume strongly influences progression free survival and time to malignant transformation. This stress the point that smaller is the tumor better is the patient outcome, and that delaying surgical intervention may increase the risk of malignant transformation.

In Berger's work, the percentage of patients in which a total and subtotal resection was achieved was 35% and 27%, respectively. These figures are in accordance of what was reported by other groups, and in our experience. This stresses the point that when brain mapping techniques are used, this results in an increase in the percentage of total and subtotal resection. For example in our series, the percentage of total and subtotal resection raised from 11% in the period in which no mapping was available, to 52.8% of the time in which brain mapping techniques were applied. When intraoperative MR was used in combination with brain mapping techniques, this resulted in a further increase in the percentage of cases in which a total resection was achieved [26].

Strategy for large, diffuse or recurrent tumors; the concept of brain plasticity

Low-grade gliomas may present as a variable type of tumors ranging from discrete and apparently well defined lesion, to either diffuse and less discrete lesion. The therapeutic strategy for the more defined type of tumors are those we previously described. Large diffuse tumors still represent a challenge. Most of them are histologically diffuse astrocytoma. The majority of these tumors contain functional subcortical tracts, and a total or subtotal resection as initial strategy is quite difficult to be achieved. Although partial removal may still be beneficial [130], particularly in those cases in which a mass effect is present, the majority of these patients underwent to stereotactic biopsy only, usually guided by spectroscopy MR images, followed by adjuvant treatments. A recent strategy to increase the rate of resection in these as well as in those tumors in which a contralateral invasion of tumor cells in visible through the corpus callosum, is represented by the use of upfront pre operative chemotherapy. Limited class IV evidence show that when TMZ is administered upfront to these tumors up to a period of six months, this resulted in a decrease in tumor cell invasion, and reduced tumor cell infiltration along large fiber tracts, such as the corpus callosum, which in selected cases may help in reach a greater percentage of tumor removal [44]. Alternatively, chemotherapy may be use as adjuvant treatment, after partial removal, and in these cases it may further decrease post

operative tumor volume till to a value of 10 ml, which from an oncological point of view is associated with a better prognosis [6, 65, 111, 116]. In addition, in case of large tumors, a two time surgical strategy may be chosen, particularly in case of large tumors involving language areas or pathways. In these cases, in which during surgery is requested a long time patient collaboration, the initial surgery is continued till the patient collaboration and responsiveness is maintained, then is resumed from one week to various months later. In our Institution we adopted the policy that a period up to four to six months is used before submitting the patient to a second surgery. This is done to get the patient to recover from the initial surgery, secondly to let the phenomenon of brain plasticity to take place [43].

Despite of aggressive and early treatment, low-grade gliomas tend to recur. As already discussed in the previous paragraph, the rate of recurrence is influenced by the pre operative tumor volume and to a lesser extent by the extent of surgical removal [10, 43, 130]. A tumor recurrence may still retain the morphological feature of low-grade gliomas, or may show signs of tumor progression, such as contrast enhancement. The appearance of contrast enhacement is usually associated with a large pre operative volume, and with the presence of limited or focal enhancement in the pre operative MR images. Generally, when a total or subtotal removal were achieved at the time of initial surgery, the recurrent tumors has a higher chance to recur still as a low grade. When only a partial removal was obtained, the percentage of recurrence toward a higher grade is much higher. When a tumor recurs, various therapeutic options are available: surgery, chemotherapy, radiotherapy, or a wait and see policy [43, 104, 116]. Surgery usually is intermingled with the other therapeutic modalities, and is the treatment of choice when a subtotal or even a total removal can be predicted, such as in case of discrete lesions. When this is feasible, the prognosis of the patient is still favourable. Brain mapping techniques can be still applicable in case of recurrent tumors, even after radiotherapy. Alternatively, surgery may be used to decrease the tumor volume, in order to enhance the effect of chemo or radiotherapy. Generally, a patient with a low-grade gliomas may undergo to several surgeries during the entire time of the disease, and surgery is used with different purposes, and strictly associated with the other therapeutic modalities [128]. Up to 30% of patients in our series underwent to 4 surgeries, and 12% were submitted up to 5 operations. We observed a decrease in extent of resection with the increase in the number of surgeries, but this was not associated with an increase in the occurrence of transient and permanent post operative deficits.

An important observation that helps in planning surgeries is the occurrence of the phenomenon of brain plasticity [45]. Cerebral plasticity could be defined as the continuous processings allowing short, middle and long-term remodeling of the neurono-synaptic organization, in order to optimize the functioning of

the networks of the brain – during phylogenesis, ontogeny, physiological learning and following lesions involving the peripheral as well as the central nervous system [45]. The occurrence of brain plasticity in low-grade gliomas has been recently known [31, 37]. Plasticity may occur in the preoperative period and in this case, it is the results of the progressive functional brain reshaping induced by these slow growing lesion. This is suggested by the fact that in the preoperative period many patients despite large tumors and extensive invasion of eloquent structures, experienced very few or no neurological deficits [45]. This is further reinforced by neuroimaging functional studies with fMRI or PET which demonstrated that areas of activation have been found also around the tumor or into the contralateral hemisphere, suggesting that the reshaping mechanisms have induced the acquisition or the unmasking of functions by areas of the brain that were previously less involved in mediating specific functions [119]. Various types of reshaping can be observed: intrinsic reorganization within injured functional areas, recruitment of other regions implicated in the functional network, in the same hemisphere (close or even far away to the damaged area), or in the contralateral hemisphere. The presence of an already existing redundancy in the functional network is also observed during the resection, when unmasking of functional activity can be observed in previous silent areas, probably due to either hyper-excitability or lowering of the activation threshold of the cortex. This is observed in the particular case of motor functions [34]. The most important observation of the occurrence of brain plasticity is the post operative period. This has been shown by submitting patients that have recovered from post operative deficit status, to functional neuroimaging studies some months after surgery and when a recovery has occurred, demonstrating the activation of different areas of the brain, close or remote to those were involved in the preoperative period [78]. Plasticity may occur either at a cortical level, or, although less frequently at a subcortical level, where it can be explained by the recruitment or unmasking of parallel and redundant subcortical circuits [40]. The occurrence of such phenomenon of compensation is of particular relevance because it allows to extend surgical indications. It allows to extend the initial surgery till when functional boundaries are encountered allowing the patient to recovering in the post operative period due to the activation of redundant functional areas, when the essential are preserved at cortical or subcortical level. Secondly, the functional reshaping induced by the initial surgery, can be used to perform a second surgery wit the aim to remove areas of the brain initially essential for function, and that due to the functional reshaping induced by the initial surgery or to the continuous slow growth of the tumor, have lost their essentiality in term of function. This functional reshaping phenomenon can be observed up to a period of six months after the initial surgery, and allows to perform a more radical second surgery with an increase in the oncological benefit for the patient. The neuro-

surgeon should gain a better knowledge of these plasticity phenomena, and their variability among patients, in order to try to integrate this potential in the surgical indications and in a dynamic surgical planning. In other words, the extent of resection and the number of surgical acts necessary to perform a tumor resection should be adapted to the individual potential of functional compensation, thus to its limits [45].

Conclusions and proposal for the future

Low-grade gliomas are slow growing intrinsic lesions that induces a progressive functional reshaping of the brain. Surgical removal of these lesions requires the combined efforts of a multidisclipinary team of neurosurgeons, neuroradiologists, neuropsychologists, neurophysiologists, and neurooncologists that all together contribute in the definition of the location, extension, and extent of functional involvement that a specific lesion has induced in a particular patient. It is important to keep in mind that each tumor has induced particular and specific changes of the functional network, that varies among patients. This requires that each treatment plan is tailored to the tumor and to the patient. When this is reached, surgery should be accomplished according to functional and anatomical boundaries, and has the aims to the maximally resect the mass and to maximally preserve patient functional integrity. This can be reached at the time of the initial surgery, depending on the functional organization of the brain, or may require additional surgeries, eventually intermingled with adjuvant treatments. The use of so called brain mapping techniques extend surgical indications, improve extent of resection with greater oncological, impact, minimization of morbidity and increase in quality of life. Data available at this time indicate that low-grade gliomas at the time of radiographic diagnosis benefit from surgery because, aggressive early surgery influences the incidence of recurrence, time to tumor progression, time to malignant transformation, and provides seizure control. Smaller is the tumor to treat at the time of initial diagnosis, higher is the possibility to reach a complete surgical resection, better is the prognosis in term of recurrence, and tendency to malignant transformation. This point stresses the need to treat smaller lesion and to reduce the time for observation. Being the diffusive nature of these tumors the main reason that mainly limit the ability to reach a complete oncological resection, the implentation at the time of surgery of imaging method such those offered by intraoperative MR, may helps to remove the tumor and to follow it along the brain. In addition, the implementation of upfront pharmacological strategies capable of reducing the invasion along white matter tracts and compacting the tumor mass, may further enhance this result. The long term oncological results of this multimodality approach requires the evaluation of a large cohort of patients. This has been recently attempted by the development of a LGG

European Network that aims both to collect data on LGG and uniform management and protocols for such tumors all across European countries.

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