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AWAKE VERSUS HYPNOSIS FOR LOW-GRADE GLIOMA SURGERY: LONG TERM FOLLOW-UP RESULT

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Illustrations

Abbreviation

AAA : Asleep-Awake-Asleep

AF : Arcuate fasciculus

EC : External capsule

EmC : Extreme capsule

EOR : Extent of resection

IFOF : Inferior fronto-occipital fasciculus

LGG : Low Grade Gliomas

MdLF : Middle longitudinal fascicle

SLF : Superior longitudinal fasciculus

UF : Uncinate fasciculus

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Summary

Part I: Generalities

1-Introduction

Low-grade gliomas (LGG) are slow-growing tumors associated with a median survival time ranging from 4 to 13 years **[1, 2, 3].**

The prognosis of LGG improved over the last two decades. Two major factors may explain this improvement. First, is the development of awake surgery, which allows a greater extent of resection while cognitive functions are better preserved. Second, is the advent of molecular biology and the better molecular classification of glial tumors, which allows clinicians to better adapt oncological treatments. The most used molecular data is IDH mutation, which is associated with a better outcome **[4].**

If the extent of resection (EOR) has already been demonstrated as a major prognostic factor of LGG, the use of intraoperative direct awake brain stimulation during surgery enables the surgeon to perform a resection according to functional boundaries, minimizing postoperative morbidity and even improving quality of life. It has also been demonstrated that this technical improvement, by allowing a better knowledge of the brain connectivity, allowed neurosurgeons to improve the EOR without cognitive impairment. Awake surgery has then also a quantitative impact on the EOR **[5].**

The classical method to perform an awake craniotomy is the asleep-awake-asleep (AAA) technique **[5].** Nonetheless, this anesthetic method might be contraindicated in some situations such as obesity or severe gastrointestinal reflux, or simply associated with a very long waking period or confusion and movements during the waking period. In a recent study **[6],** we demonstrated the reliability of hypnosis as an original alternative method for performing a

craniotomy during awake surgery. In this previous work, although we did not demonstrate any superiority of hypnosis on the "classical" AAA method, which remains, in our opinion, the gold standard for resection of LGGs in young adults **[6],** we showed that hypnosis allowed an effective awake mapping for glioma resection with no negative psychological impact.

Our objective in this new study was to assess the impact of hypnosis on the oncological performance of awake surgery of LGG. We reviewed the preoperative tumor characteristics, the residual tumor volume, post-operative course (clinical and radiological follow-up, oncological treatment), and survival data on our monocentric series of patients that had undergone awake surgery for a low-grade glioma, with either hypnosis or AAA.

2-Awake craniotomy and Brain mapping History

The idea of awake craniotomy for tumor surgery arose from its use for epilepsy surgery **[7]**. Thousands of years according to archaeological discoveries treatment of convulsion by trepanation of the skull, Hughlings Jackson, conducted an extensive study of local epilepsy between 1864 and 1870 **[8, 9]**, predicted that an area existed in the cerebral cortex that governed isolated movements. This was verified by Fritsch and Hitzig in 1870, who for the first time was able to induce extremity movements in animals by means of electrical stimulation on the cerebral cortex **[10]**. Besides, the first concept of brain mapping with electrical stimulation in humans was generated by Bartholow in 1874 **[11]**. He used an electrode to stimulate the cerebral cortex through a skull abnormality resulting from bone infiltration of an epithelioma. A decade later, in 1886, Horsley, whose animal studies gave him an excellent understanding of the human cortex **[12]**. In the late 1920s, Wilder Penfield was trying to treat patients with refractory epilepsy **[13]**. He also applied a gentle electric current to map the brain. He concretely described the technique of stimulation while patients were awake to alert. He applied this to some brain tumor patients, including his own sister **[13]**. Recently, the mapping by DES was obtained by applying a biphasic current of the bipolar electrode, especially 1 to 6 mA for local anesthesia and 4 to 18 mA for general anesthesia. It can be controlled by either voltage or current as of the parameter of optimization for the brain **[14]**.

Part II: Reminder

1-Cortical Functional Areas

The cerebral cortex is a mosaic of specialized regions controlling specific primary functions, the cortical areas.

Cortical functional areas are specific centers in the cerebral cortex responsible for processing and programming nerve impulses. They have been described by Brodman according to their functional role based on histological sections encompassing the entire cerebral cortex. These areas are interdependent thanks to the associative fibers which give the brain immense functional possibilities **[15]**.

1.1-Somesthetic areas

These areas are subdivided into primary and secondary

1.1.1-PRIMARY

We have three areas (Somato-sensory cortex) which are named respectively area 1, area 2, area 3. They occupied the postcentral gyrus (Figure 1). Area 1 receives the impulses of superficial sensitivity, area 2, those of deep sensitivity, the area 3, those of painful sensitivity **[15]**.

1.1.2-SECONDARY

The secondary areas are named area 5 and area 7. They are located in the first anterior part of the parietal lobe P1. Area 5 and area 7are the associative somatosensory area, which allows coordination of movements according to visual-proprioceptive data **[15]**. **(Figure 1)**

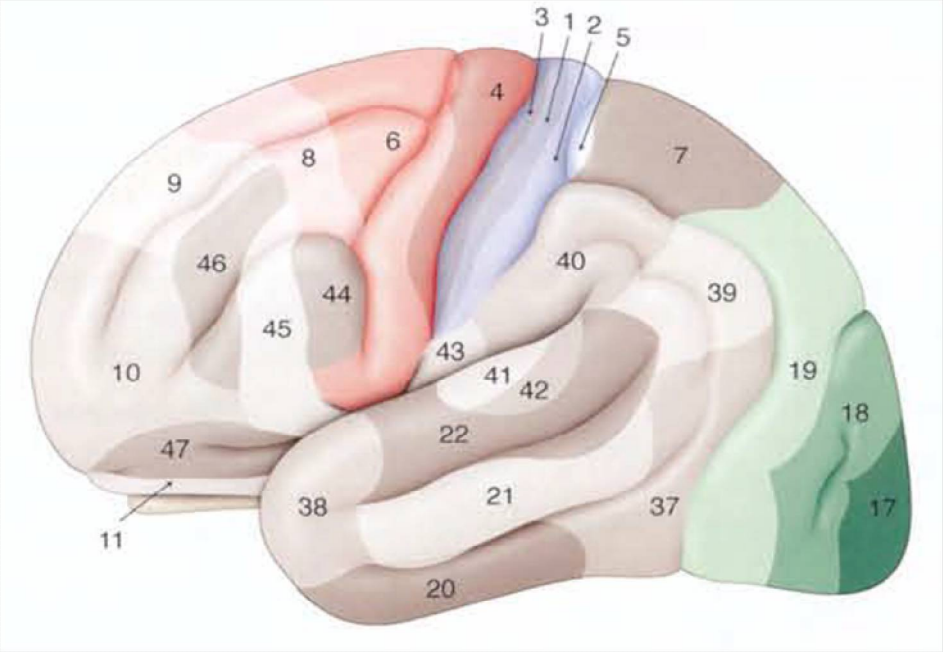


Figure 1: Somesthetic Areas (1,2,3,5,7) **[15].**

1.2- Primary Motor Area

The primary motor area is named area 4, it is the primary somatomotor cortex which is located in the precentral gyrus (Figure 1). This area controls voluntary motor skills, its efferents form the pyramidal tract which constitutes the direct motor pathway whereas its afferent fibers come from the thalamus, the premotor areas, and the somatosensory cortex. Besides, its somatotopic subdivisions correspond to a part of the body according to Penfield. The Motor Homunculus designates the organization of motor control of the muscles of the human body on the surface of the brain. The sensory homunculus or somesthetic homunculus corresponds to the cortical areas of somesthesia**[15]**. (Figure 2)

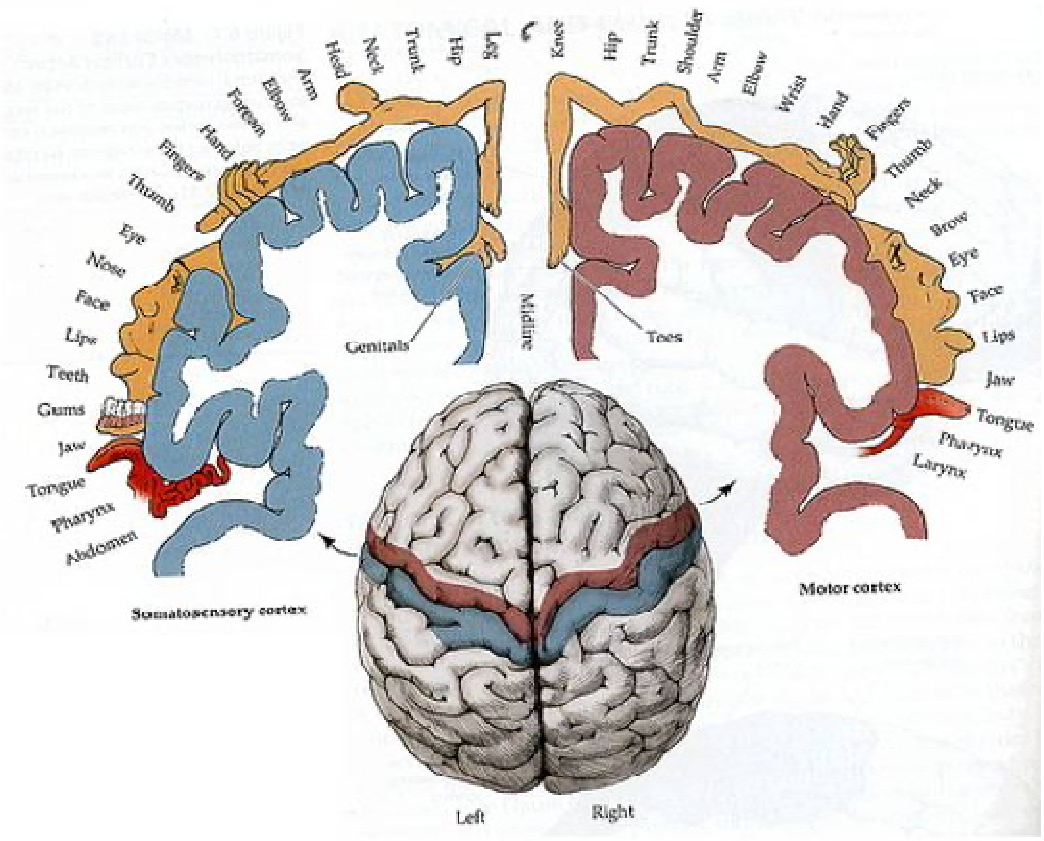


Figure 2: Penfield Homunculus **[16]**

1.2-Secondary Motor Areas

The secondary motor areas(Premotor Cortex) are named areas 6 and area 8. Area 6 is the premotor area and medial supplementary motor area, and area 8 is the frontal oculomotor field, responsible for eye movements. These areas are located in the superior and middle frontal gyrus, control balance, motor spasticity, and ocular-cephalic coordination. Its efferent fibers form the extrapyramidal tract which constitutes the indirect motor pathway. Its afferent fibers arise from the thalamus, basal nuclei, and cerebellum **[15]**. (Figure 3)

1.3-Tertiary Motor Area

This area is named area 46, it is the dorsolateral prefrontal area which is located at the F2 level and contributes to Judgment, attention, working memory skills. (Figure 3)

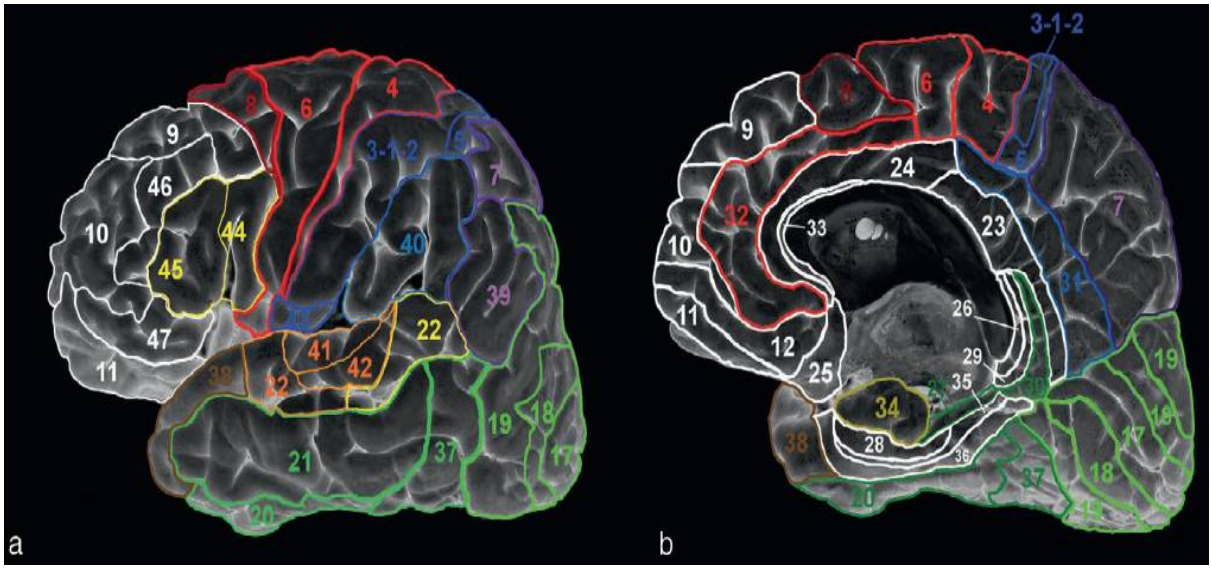


Figure 3: Primary, Secondary, tertiary motor areas and languages areas, sensory areas, tasting areas, olfactory and hearing areas (4,6,8, 17,18,19,22,25,28,34,39,40,41,42,43,44,45,46) **[16].**

1.4-Language Areas

At the level of the left cerebral hemisphere in the right-handed person, the language areas are named Broca's areas 44-45 for the expression language skills which are located at the level of the cape and the foot of F3(Frontal Lobeb Part 3). These areas control speech motor programming (articulate language) whereas the written language is covered by part of Area 8 (secondary motor area)**[15, 16]**. (Figure 3)

It is important to remind also the language understanding written area (area 39) which is located at the level of angular gyrus, the posterior third of Wernicke's area. This area is visual area is responsible for the understanding of the image. Besides, the oral language is covered by area 22 (verbal auditory area) which allows understanding of sound, and area 40 which is located at the level of supramarginal gyrus, the upper third of Wernicke's area, Its function is the understanding of the gesture that accompanies oral language **[16]**. (Figure 3)

1.5-Sensory Areas

The sensory areas are the visual areas(17,18,19), tasting areas(43), olfactory areas(25,28,34), and hearing areas(22,41,42).(Figure 3)

The visual area is area 17 (primary visual area) which is located on either side of the calcarine fissure on the median face. the areas 18 and 19 are associated visual areas and located on either side of area 17. The tasting area (area 43) is located in the subcentral area of the insular lobe, the olfactive areas are the posterior entorhinal area (area 28), the anterior entorhinal area (area 34) which are both located in the parahippocampal gyrus, and the septal area (area 25) which located below the corpus callosum. The primary hearing (area 41) is

located above T1 near the fissure of Sylvius, then the associative hearing area (area 42) on the periphery, around area 41, whereas the area 22 which is also the associative hearing area located in the cerebral hemisphere dominating at the level of the posterior part of the superior temporal gyrus and overflowing on the angular and supramarginal gyrus **[15, 16]**. (Figure 3)

2-Cerebral Connectivity

Three main bundles ensure the fronto-temporal connectivity involving the Broca language area. we have the Arcuate fasciculus (AF), Extreme capsule (EmC), and Uncinate fasciculus (UF). There are several pathways anatomically detectable, which constitute connections between language-related areas and may therefore be functionally important in language tasks **[17,18]**.

The major fiber tract of the dorsal stream is the AF and the major tract of the ventral stream is the IFOF. (Figure 4, Figure 5) However, the assignment of a specific function to a distinct fiber tract is rather critical. Generally speaking, white matter fiber tracts represent reciprocal connections between distributed gray matter regions in the brain **[17]**. Fiber tracts are composed of axons and the axon is a part of a neuronal cell. Thus, a lesion of the axon leads to changes of the axonal structure distally to the lesion causing Wallerian degeneration, but also proximally to the lesion in the soma of the nerve cell (Axer, Axer, Gräßel, & Witte, 2008) **[19]**. White matter tracts establish a spatially defined network that determines function (Hickok & Poeppel, 2000) **[20]**. Therefore, fiber tracts cannot have a function on its own, they are part of a topographically distributed network system. Disruption of fiber connections will consequently cause

structural and functional changes in directly and indirectly connected gray matter areas. Because language function is assumed to be the result of parallel distributed processing of connected neurons (Duffau, 2008)**[21]**, fiber disconnection could therefore cause widespread functional disturbances within this neuronal network. The language function is, therefore, the result of parallel distributed processing of connected neurons (Duffau, 2008)**[21]**. A possibility to selectively disturb the function of defined fiber tracts in the human brain is intraoperative electrical stimulation during neurosurgical interventions in awake patients. Hereby, it could be demonstrated that electrical stimulation of AF and insulo-opercular connections generated anomia (Duffau et al., 2002) **[22]**.

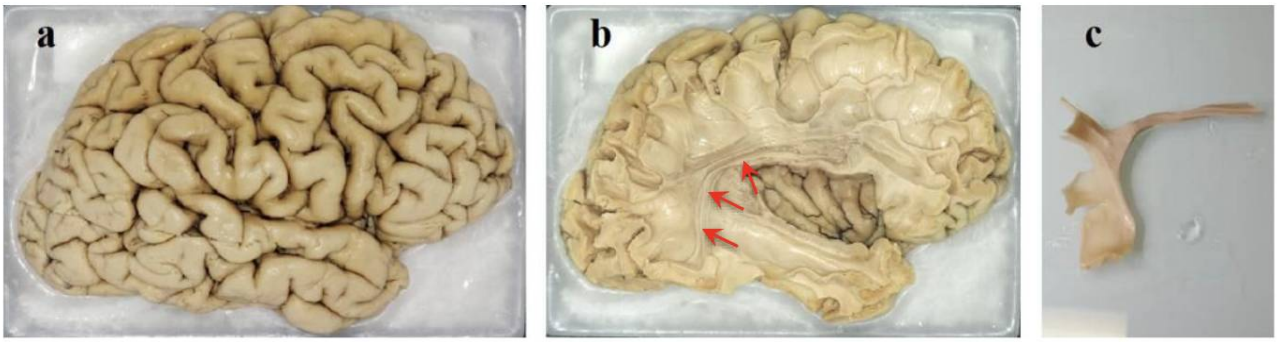


Figure 4: Dissection according to Klingler's method of the cerebral white fibers of a right hemisphere. (a): cerebral cortex in place; (b): visualization of the arcuate bundle (arrows); (c): isolated arcuate beam segment showing that it is possible to loosen the fibers. Anatomy laboratory, François-Rabelais University of Tours **[18].**

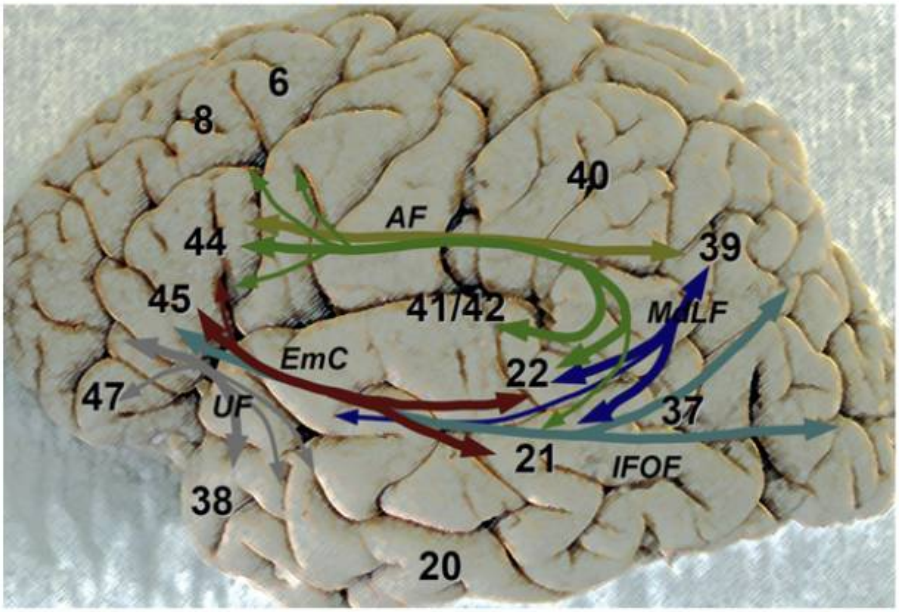


Figure 5: Connectivity scheme of human language-related areas **[17]**.

2-Clinical manifestations of LGG

Seizures are the commonest presentation and may be partial or generalized. They occur in over 90% of patients and are intractable in 50% **[23]**. Seizures are more frequently associated with cortically based tumors, particularly in frontal, temporal, and insular/parainsular locations, and with oligodendroglial tumors **[24]**. There is no clear association between the severity of epilepsy and the behavior of the tumor. Focal neurological deficits are unusual, developing over many years. Raised intracranial pressure is rare in patients with supratentorial tumors and is typically seen in the posterior fossa and intraventricular tumors. Intratumoral hemorrhage can occur **[24]**.

3-Paraclinical Diagnosis of LGG

Conventional MRI is useful for differential diagnosis, guiding biopsy or resection, planning RT, and monitoring treatment response **[25]**. LGGs appear as low-signal mass lesions on T1-weighted MRI and high signal on T2-weighted and FLAIR sequences. Contrast enhancement is usually absent; when present, it may indicate a focal area of high-grade transformation, although some tumors, particularly oligodendrogliomas, have patchy enhancement, which remains stable over time **[25]**.

Proton Magnetic Resonance Spectroscopy (MRS)measures major metabolites in tumor tissue. The typical spectrum of an LGG shows elevated choline, reflecting increased membrane turnover, and decreased N-acetyl-aspartate, reflecting neuronal loss, but similar abnormal spectra may be seen in non-neoplastic lesions **[26]**. Grading of gliomas is not possible by spectroscopy

alone, as there is considerable overlap between low-grade and high-grade lesions. The presence of lactate and lipids is associated with higher proliferative activity and more aggressive behavior **[26]**. MRS is helpful in guiding a biopsy to an area of high-grade activity, but not in longitudinal monitoring **[27]**.

4-Awake Craniotomy Indications

Awake craniotomy is used for any intra-axial mass lesion residing beside or in an eloquent brain based on imagery, including the motor and language cortex, and also cortex responsible for other functions, for example, executive functions of the frontal or temporal lobe **[28, 29, 30]**. Mainly gliomas, cortical and subcortical, both high and low grade, as the survival rate is related to the extent of resection. Intraoperative stimulation mapping in an awake patient can also be used in refractory epilepsy, as extratemporal epileptic foci are often close to eloquent brain areas; vascular lesions (eg, arteriovenous malformation) near eloquent areas **[31]**.

5- Absolute Contraindications

-Patient refusal, **[31]**

-Dysphasia, confusion, drowsiness, cognitive impairment (dementia, Down syndrome), unable to sit still for long periods **[32]**,

-Claustrophobia, mood swings **[32],**

-Uncontrolled cough, morbid obesity, obstructive sleep apnea **[32],**

-Large and highly vascular tumors, middle fossa floor injury (awkward position ± dural pain) **[32],**

-congestive heart failure (ejection fraction <10%) **[33]**,

-3rd-trimester pregnancy with impending neurological crisis **[34]**, age range from 9 to 90 years old **[35].**

Part III: Awake craniotomy with type of sedation technics

1-Awake craniotomy technics

1.1-Psychological Preparation

The patient will be seen prior by the physiotherapist for physiological tests as well as tasks to be carried out. Awake craniotomy requires skill, experience, and commitment from the entire operating room team. Training with patients for all team members is key to building trust and commitment. Surgeons, anesthesiologists, and nurses provide comfort and empathy to the patient, alleviating their anxiety. Patients should be informed about constant face-to-face interactions and other details, and compare positioning, indwelling urinary catheter insertion, craniotomy noise, and mapping tasks **[36]**.

1.2- Premedication

Pre-medication should be individualized based on the patient's condition and needs. In general, certain medications should be avoided or used with caution, such as midazolam, atropine, and scopolamine, because they can impair neurocognitive function and lead to confusion or delirium. However, a small dose of midazolam (1 to 2 mg intravenous [IV]) is beneficial in young, highly anxious patients with normal preoperative neurological function. Patients with seizure mapping should not receive any drugs that suppress epileptiform activity, eg, midazolam, anticonvulsants **[31]**. There is no consensus on the need to administer anticonvulsants in patients without previous seizures.

1.3-Monitoring and surgical Position

Monitoring

Standard monitoring include an electrocardiogram, oximetry, non-invasive and intra-arterial blood pressure, respiratory rate, and urine output. Monitors should be placed on the same side as the brain injury to avoid interfering with the monitoring of contralateral sensorimotor functions.

Positioning

Patients are typically lateral or semi-lateral, rotated 90 degrees to the anesthesia workstation, and facing the anesthesia team to allow for face-to-face interaction and airway management. The head is usually secured in a Mayfield point header after anesthesia **[31]**.

1.4-Anesthesia for Asleep phase for craniotomy

Currently, several techniques are used in clinical practice, including hypnosis described recently in 2015. (ref) Mainly two methods are described: Asleep – Awake – Asleep/ Awake-awake-awake **[31],**(ref)

(1) Asleep–Awake–Asleep: Patient will have general with laryngeal mask airway/endotracheal tube (LMA/ETT) for craniotomy and closure but awake and extubated for mapping and resection.

(2) Awake-awake-awake: The patient will be awake with sedation (light, moderate or deep) with ventilation for the craniotomy and closure **[31]**.

(3) Hypnosis for sedation: The patient will be hypnosedated for craniotomy without intubation (cf detailed procedure)

With these three approaches, no medication is typically administered during the mapping phase. The choice of anesthesia technique should consider team preference, tumor location, status, body size, age, motivation, and medical comorbidity in addition to the patient's physical condition.

1.5-Detailed Hypnosedation Procedure (http://links.lww.com /NEU/A772)

Patients were positioned on a smooth foam mattress. Hypnotic trance was induced by eye fixation. Throughout the trance, instructions were repeated: “lachez prise” (the French translation of “let go”), “faites confiance en vous-même” (trust yourself), “profitez des instants” (enjoy the moment). At the beginning of the trance, the patients had to separate the mind and the body and maintain a distance of 2 cm between them. They were told that their unconscious was involved, that splitting the mind and the body would highlight the connections that usually join them, and that they should separate them. During this exercise, they were asked to fold these connections in three and place them in their right foot; this would protect the body and place it under the control of the unconscious; in this way the body was safe. A peripheral venous catheter and an arterial radial catheter were then inserted, and the metaphor of an insect flying and gathering nectar was suggested, after which Remifentanil 1 ng/ml was continuously infused (with a target control infusion mode, which potentialized the hypnotic trance).

Boli of Propofol 10 mg were performed when the patients experienced a difficult time, which allowed the patients to easily “let go” without modifying consciousness: the patients continued to hear the voice of the hypnotherapist. A

bladder catheter was then inserted, with the metaphor of colored energy with heat in the lower body. To enter the hypnotic trance more deeply, the patients were asked to increase the distance between the mind and the body to four cm and to fold the new connections in four and place them in their right foot.

The patients were then positioned in lateral decubitus while continuing to use the metaphor of colored and warm energy. When the Mayfield head clamp was placed, the metaphor of energy was used again. Briefly, patients were told that this energy was circulating along the spine to form a sphere around the back of the neck, and they were encouraged to let their minds float above and around their bodies at a distance of six cm. The last connections appearing between the mind and the body had to be folded very carefully in six and separated from the others. Next, the sphere of energy had to be divided into three other spheres that had to be placed around the skull. During these 2 displacements, the three spheres changed color and temperature. When the spheres had been established around the skull, the Mayfield clamp pin sites were infiltrated with Lidocaine. When the head clamp was placed, the patients were warned that they would feel pressure.

To add a sense of mystery, three mystic cardinal points were described. The cranial nerves (supraorbital, temporal, auricular, and occipital) were blocked with ropivacaine and the incision was infiltrated with Lidocaine mixed with saline serum 0.9%, while the metaphor of a migration of energy to build connections between the three cardinal points was suggested. During the placement of the operating fields and skin incision, the hypnosis focused on relaxation. A series of words were repeated, “poser, composer, decomposer” (“put down, put together, break down”), or a series of random numbers. During

the burr hole drilling and saw cutting (bone flap), the patients were asked to imagine a vibrating device, for example, they were on a bicycle with triangular or square wheels. While the bone flap was being lifted, the patients were instructed to cough. The trance ended during the opening of the dura mater. A new phase of relaxation was induced and the metaphor of the mind separated from the body was used again, but this time to bring the mind back into the body to end the trance. The patients then returned to full consciousness for the awakening phase **[6]**.

1.5-Awakening phase.

The goal is to transition smoothly and quickly without restlessness, the patient should be engaged, cooperative, painless, and comfortable for tumor mapping and resection. All agents are stopped, although it is sometimes helpful to keep a low dose of remifentanil (0.01–0.05 mg/kg/min or 0.2–1 ng/mL), give small doses of fentanyl for analgesia. Pain should be managed with local analgesia and possibly IV acetaminophen **[31]**.

Medication avoidance during intraoperative management reduces fear and anxiety. Empathy, handshake, reassurance, encouragement, coaching, and conversation are all helpful and important.A sponge soaked in ice water can be used to wet the lips and comfort the patient's mouth. The patient may be allowed to move their limbs and hips at appropriate times. An air blanket is used to provide hot or cold air to maintain a comfortable temperature. Then the brain mapping will start **[31]**.

1.6-Intraoperative physiological test for Brain Mapping

Motor and sensory pathways

Awake surgery provides a precise mapping of the superficial and deep pathways of the limbs, face, and mouth. Mapping can cause or inhibit movements. Responses from orofacial musculature, laryngeal activity, and vocalizations may be recorded by the speech therapist as tingling or movement, for example, tongue withdrawal or speech stops.Also, tingling, jerking, or movement in the limbs may be caused, most commonly by the arms and hand. The speech-language pathologist should carefully observe the patient and report every movement to the surgeon, and the patient should also be instructed to report any abnormal movement or sensation. Stimulation mapping not only allows cortical delineation (cortex) but also allows the surgeon to stimulate and monitor subcortical pathways using electrodes **[37]**.

Language

To assess speech, the visual object naming test is frequently used. The Boston Naming Test includes 60 drawings of common objects graded in difficulty, eg, window, car, dog, guitar. Bilingual patients should be tested in both languages as the anatomical areas may not overlap entirely. The electro-stimulation is done using bipolar electrodes separated by a distance of 5 mm with a 60 Hz single-phase of 1 ms. The first stimulation intensity is 2.5 mA, then it was increased by 0.5 mA until a negative motor response was triggered **[38, 39]**.

Visual.

Intraoperative brain mapping of the cortical visual cortex with subcortical visual pathway mapping may be helpful in minimizing the risk of permanent hemianopia tumors located in the parieto-occipital region. Identification of optical radiation by direct subcortical electrostimulation is a reliable method to reduce permanent glioma surgery damage involving visual pathways **[40, 41]**.

Methods to identify other functions such as memory and counting are of interest and are under development.

1.7-Tumor Resection

It is done using the ultrasonic vacuum cleaner respecting the borders delimited by the mapping of the functional areas while the physiological test continues to be exercised by the patient and the speech therapist under the monitoring of the anesthesiologists. Excision should be as wide as possible or even complete as far as possible, especially in the case of low-grade gliomas. Surgical resection and excision should be stopped when active functions have been identified intraoperatively by direct electrostimulation. The tumor piece should then send to the pathologist for biomolecular testing.

1.8-Post-awakening phase

Similar to the pre-awake phase, one can also choose awake and spontaneous ventilation under light or deep sedation or GA with airway control. Sedation alone is often sufficient. The patient generally requires lower rates of sedative infusions during the post-awakening phase than during the pre-awakening phase because patients are often fatigued, and there is a lower level of painful stimuli during skull closure **[31]**.

1.9-Postoperative care.

The patient must first be admitted to a neurosurgical continuing care unit or to neuro-resuscitation. Pain management can be achieved with small doses of intravenous opioids, controlled analgesia, oral opioids combined with acetaminophen **[42]**.

2-Challenges and complications of Awake craniotomy

Challenges during the awakening phase **[31]**.

Common challenges: include hypertension, seizures, drowsiness, restlessness, oxygen desaturation, brain tightness, and chills **[31]**.

Nausea and vomiting: These are most commonly associated with opioids; other common associated factors are age, gender, and anxiety. The incidence is much lower with routine use of propofol. Management includes empathy, ondansetron, and small dose propofol (20 to 30 mg).

Hypothermia and chills: these should be avoided by using blankets, hot air devices, and appropriate room temperature **[43]**.

Postoperative complications

Common to all cranial surgery: Infections, Hematoma of the operating hearth, Extradural hematoma (rare), and Seizures.

Part IV: Methods

Ethics Statement

The data collected during the study have been stored in a computer file following the law of the French Data Protection Act of January 6, 1978, amended in 2004.

Study Population

Between May 2011 and December 2019, all the patients that had undergone an awake craniotomy, either with hypnosis or with AAA procedure, for the resection of an LGG in our institution, were included. All patients who were diagnosed with a high-grade glioma were excluded. Our series included 69 consecutive patients according to these criteria. Clinical, radiological, surgical, biological, treatment, and survival data were collected retrospectively into a database.

Clinical patient information included age, gender, date of diagnosis, location of the tumor, date of surgery, preoperative tumor volume, post-operative residual tumor volume on 3- or 6-months postoperative MRI, histopathological diagnosis, molecular data, and long-term follow-up features.

Methodology used to measure tumor volume

We used preoperative and postoperative (3 to 6 months after surgery) FLAIR MRI sequences to visualize tumors that all appeared as a hyperintense mass. We then used the open-source software ITKSNAP 3D Segmentation (v.3.4.0 US national institute of health) to semi-automatically segment the tumors (manual thresholding, manual placement of seeds in the regions of interest, 3D automatic expansion of the seeds, and manual correction of the segmentation obtained). (Figure 4)

We empirically stratified the preoperative volume in three groups (< 20 mL, 20 to 40 mL, and > 40 mL), the residual tumor volume was stratified in two groups (<3cc and ≥ 3cc), and the EOR was also categorized as ≥ 95% or < 95%.

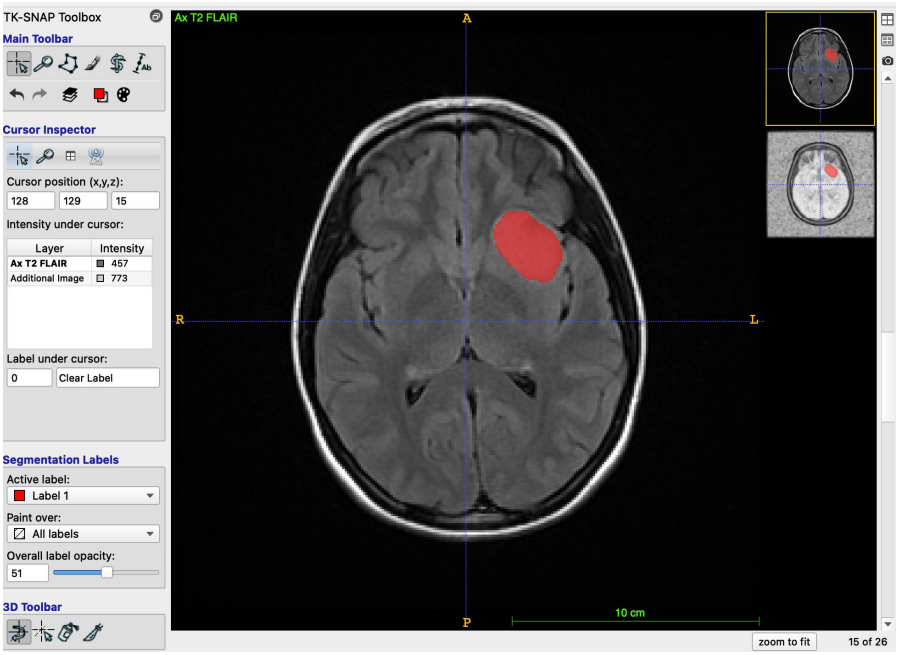


Figure 6: FLAIR Axial view 3D segmentation for measuring the pre-operative LGG volume with ITK-SNAP Software

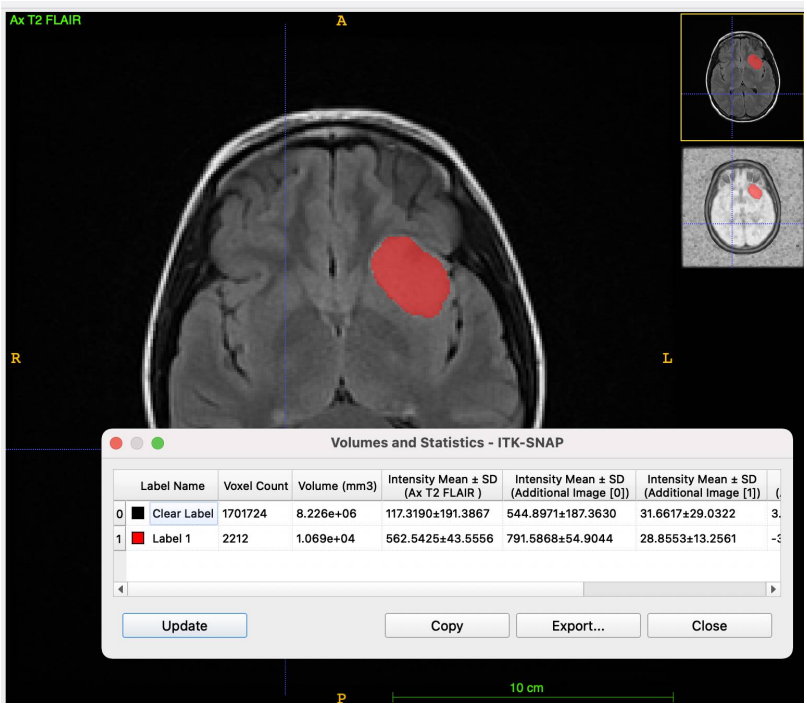


Figure 7:3D volume acquisition after segmentation with ITK-SNAP Software

Statistical analysis

Statistical analyses were performed with Excel and SPSS v. 26 (IBM, USA). The Pearson Chi-square, Fisher exact, and Mann-Whitney U tests were used to evaluate correlations and associations. Data are presented as the mean +/- standard deviation. For all analyses, P-values < 0.05 were considered statistically significant. We used Kaplan Meier curves to analyze survival.

Part V: Results

Sixty-nine patients aged 40.80 (SD=12.06) years were included. 2015 and 2016 had the highest annual frequencies (20.29% each). (**Figure 8**) Most patients were male (n=36, 52.2%) and LGGs were usually limited to a single brain region (n=48, 69.57%). Most tumors were located in the frontal (n=47, 68.12%), temporal (n=17, 24.64%), and insular (n=11, 15.94%) lobes. Twenty-eight patients (40.58%) were hypnosedated while 41 (59.42%) received standard AAA. Women were predominantly present in the hypnosis cohort with respectively 16/28 (57.14%) vs 17/41 (41.46%) (p = 0.20 and OR = 0.5 [0.2-1.4]). **(Figure 9)**

Fifty-five patients (79.71%) had IDH mutated tumors and 14 (20.29%) had IDH wild type tumors. Three cases (4.35%) were diagnosed with a grade I glioma, one case of them was a DNET (Dysembryoplastic neuroepithelial tumor) and the 2 other cases of them were PGNT (papillary glioneuronal tumors). Most tumors had a preoperative volume >40 mL (n=35, 50.72%) and a postoperative volume ≥ 3mL (n=40, 57.97%) (**Table 1**). Median preoperative tumor volume was 40.36 mL(IQR=62.34 mL) and median residual tumor volume 3.90 mL (IQR=11.71 mL).

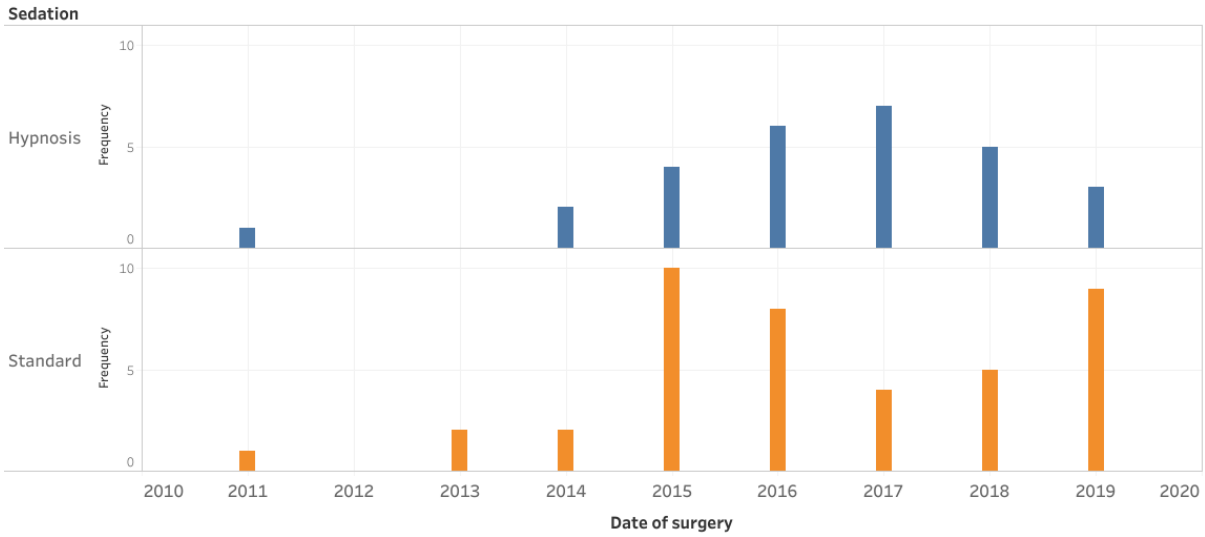


Figure 8: Annual repartition of low-grade glioma awake surgeries with hypnosedation and standard asleep-awake-asleep procedure in our cohort

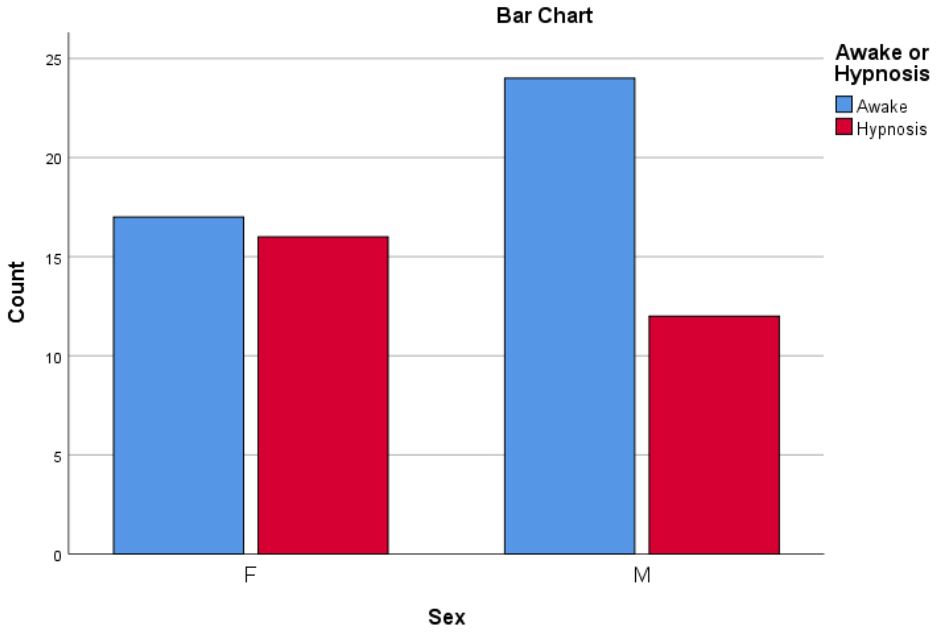


Figure 9: Distribution of sex between Asleep-Awake-Asleep (Awake) and Hypnosis cohort.

Table 1: Descriptive characteristics of patients

Characteristic	**Frequency (Percentage)**
Sex	
Female	33 (47.83)
Male	36 (52.17)
Number of brain regions invaded	
1	48 (69.57)
2	12 (17.39)
3	9 (13.04)
Location	
Frontal	47 (68.12)
Temporal	17 (24.64)
Insular	11 (15.94)
Parietal	8 (11.59)
Callosal	7 (10.14)
Cingular	6 (8.70)
Occipital	3 (4.35)
Preoperative volume	
<20 mL	22 (31.88)
20-40 mL	12 (17.39)
>40 mL	35 (50.72)
Postoperative volume	
<3mL	29 (42.03)
≥ 3mL	40 (57.97)
Biomolecular profile	
IDH+	55 (79.71)
IDH+ 1p19q -	30 (43.48)
IDH+ 1p19q +	25 (36.23)
IDH-	14 (20.29)
Sedation	
Hypnosis	28 (40.58)
Standard	41 (59.42)

Asleep-Awake-Asleep vs. Hypnosis:

The hypnosis-aided surgery cohort had more LGGs with tumor volumes >40 mL (64.28% vs. 41.46%, P=0.035). However, we did not find evidence of a difference in the residual tumor volume between the two groups (32.14% of hypnosis-aided surgery tumors were <3mL vs. 48.78% for standard AAA surgery, OR=0.5, 95% CI=0.18-1.35, P= 0.17).

The median extent of resection was 85.70% (IQR=23.50%); 54 patients had an extent of resection <95% (78.26%). Forty-three patients (62.32%) were operated on once, and 26 (37.68%) needed redo surgery. Two patients (2.90%) were lost to follow-up, and eight patients (11.59%) died. We found no evidence of a difference between the hypnosis-aided and standard AAA surgery (P=0.51) (**Table 2**).

Table 2: Outcome comparison between hypnosis-aided and standard asleep-awake-asleep surgery for low-grade gliomas

Characteristic	**Total (%)**	**Hypnosis (%)**	**Standard (%)**	**P-value**
Preoperative volume				
>40 mL	35 (50.72)	8/28 (64.28)	17/41(41.46)	**0.035***
Postoperative volume				
< 3 mL	29 (42.03)	9/28 (57.14)	20/41(41.46)	0.17
Extent of resection				
100%	2 (2.90)	0	2 (2.90)	
95-99%	13 (18.84)	8 (11.59)	5 (7.25)	0.51
<95%	54 (78.26)	21 (30.43)	33 (47.83)	
Number of redo surgeries				
1	19 (27.5)	5 (7.25)	14 (20.29)	
2	6 (8.69)	3 (4.35)	3 (4.35)	
3	1 (1.45)	0	1 (1.45)	0.37
Sequelae				
Seizures	14 (20.29)	8 (11.59)	6 (8.69)	
Language deficit	8 (11.59)	3 (4.35)	5 (7.25)	
Altered level of consciousness	1 (1.45)	0	1 (1.45)	0.63
Disequilibrium	1 (1.45)	0	1 (1.45)	
Dysexecutive syndrome	1 (1.45)	0	1 (1.45)	
Memory deficit	1 (1.45)	0	1 (1.45)	0.44
Death	8 (11.59)	4 (5.80)	4 (5.80)	0.31
Loss to follow-up	2 (2.90)	0	2 (2.90)	

Overall survival

Patients in the standard AAA surgery group had longer survivals than those in the hypnosis cohort (93% and 88% of patient in the AAA surgery group reach respectively 5 years and 10 years OS versus 92% and 72% in hypnosis cohort) (P=0.44). (**Figure 10**)

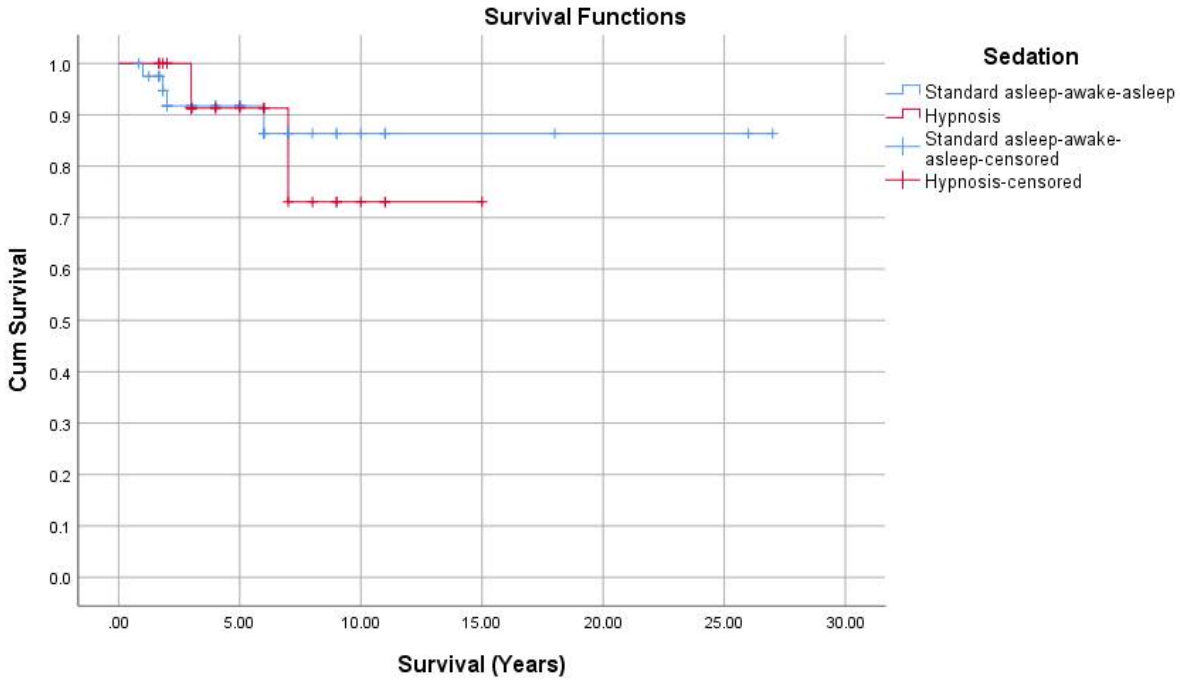


Figure 10: Kaplan Meier survival curve comparing the standard asleep-awake-asleep sedation cohort with the hypnosis cohort.

IDH+ 1p19q - and, IDH+1p19q+ patients had a long overall survival than IDH- patients (100% and 82% of the IDH+1p19q-patients reach respectively 5 years and 10 years OS , 92% and, 82% of IDH+1p19q+ patients versus 74% and 74% in IDH- patients).(**Figure11**)

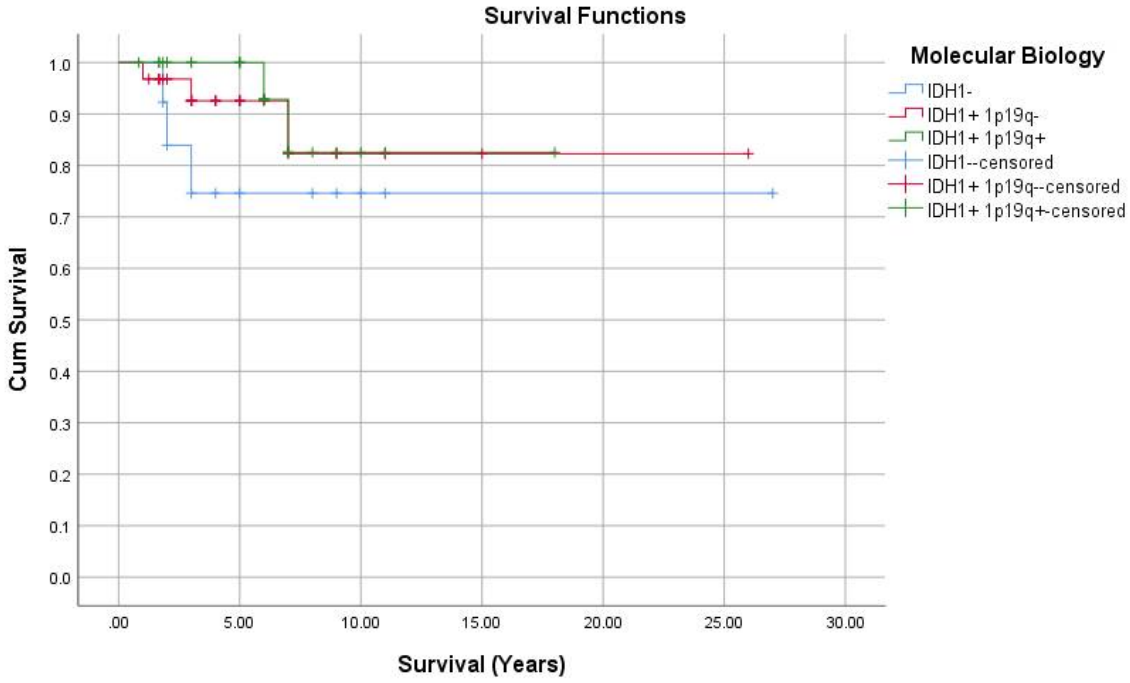


Figure 11: Kaplan Meier survival curve disaggregated by IDH status.

When comparing survival, we found clinically significant differences between pre-and postoperative tumor volume and extent of resection groups. The overall survival time in patients with preoperative LGG volumes ≤ 20 mL was longer (95% of patients with LGG volumes ≤ 20 mL reach 5 years and 10 years OS, *vs* 92% and 65% of patients with LGG volume ≥ 20 mL)**(Figure 12)**.

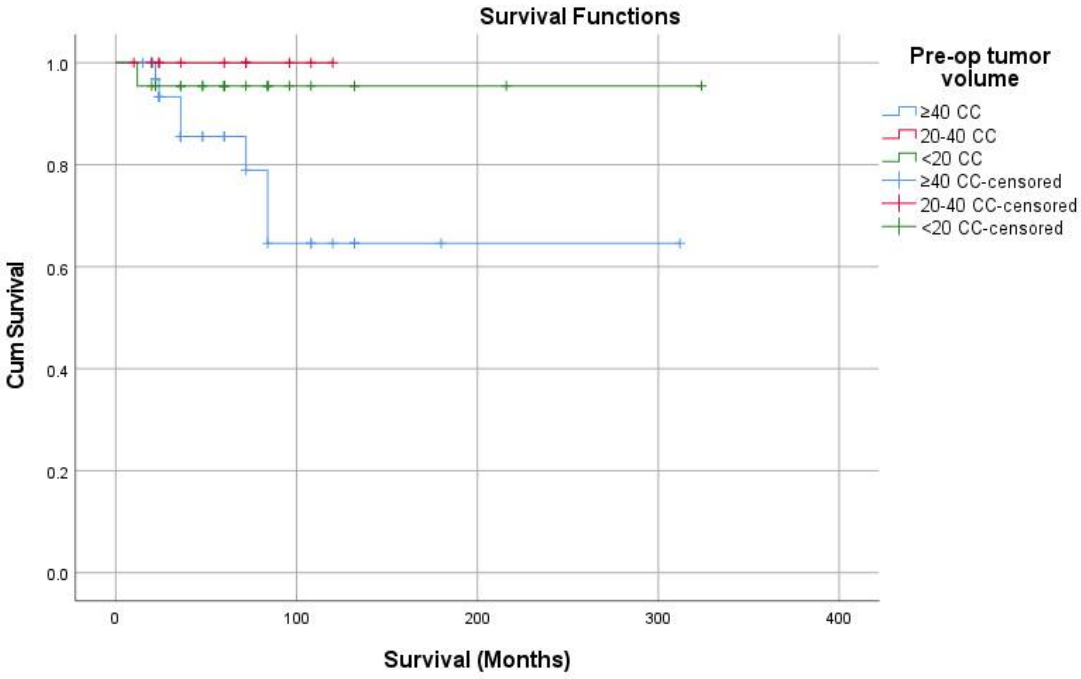


Figure 12: Kaplan Meier survival curve disaggregated by Preoperative volume.

Also, the 5 years and 10 years OS for LGGs with a residual volume < 3 mL was reached respectively in 100% and 92% of patients while LGGs with a residual tumor volume ≥ 3 mL had reached 5 years and 10 years OS in 84% and 72% (**Figure 13)**.

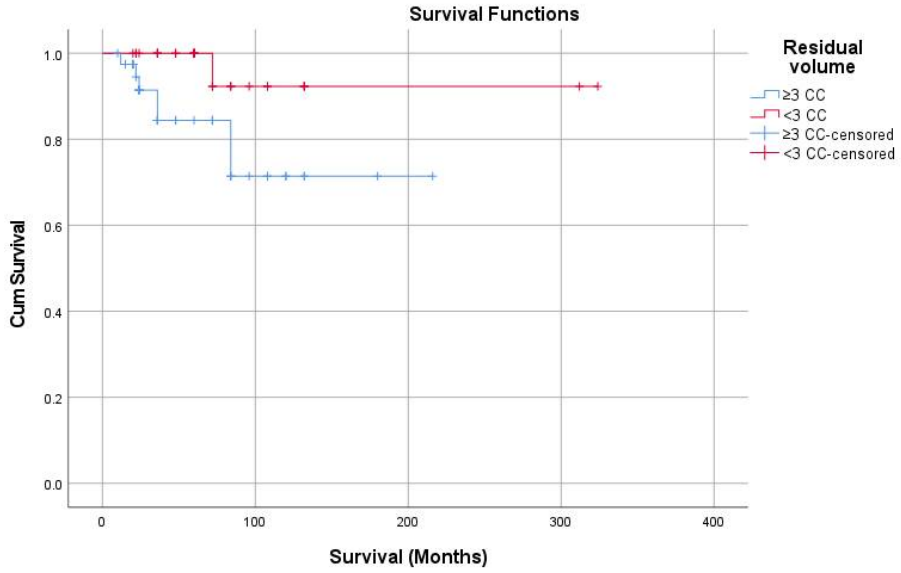


Figure 13: Kaplan Meier survival curve disaggregated by Residual Volume postoperative.

Finally, patients with an EOR ≥ 95% survived longer than those with an extent resection < 95% (100% and 87% of patients with an EOR ≥ 95% reached respectively 5 years and 10 years versus 89% and 78% in patients with an EOR < 95%) **(Figure 14)**.

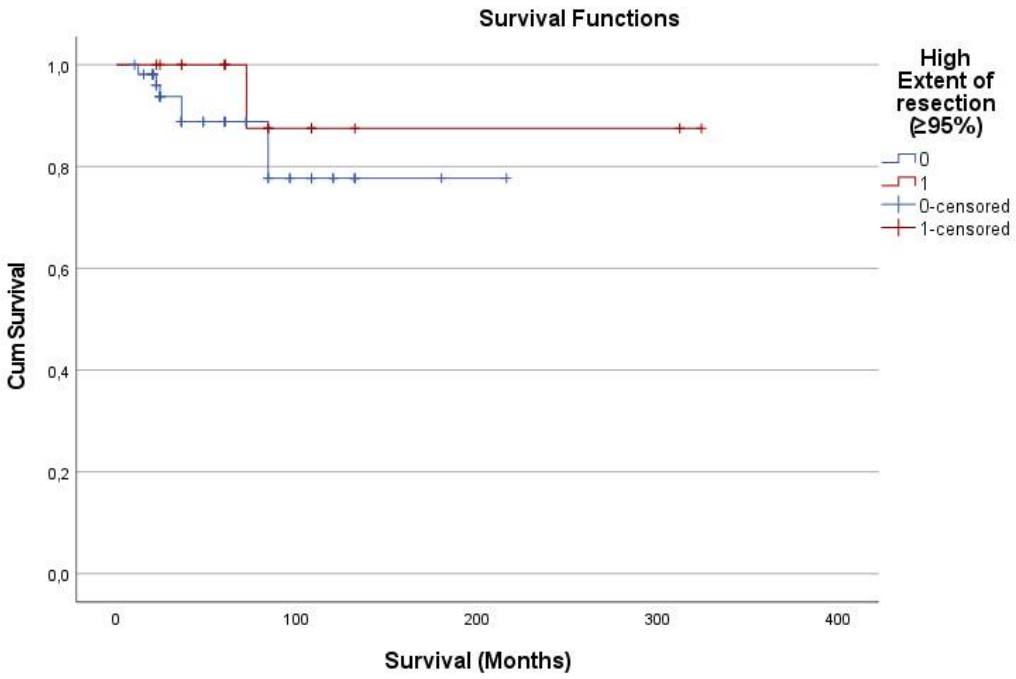
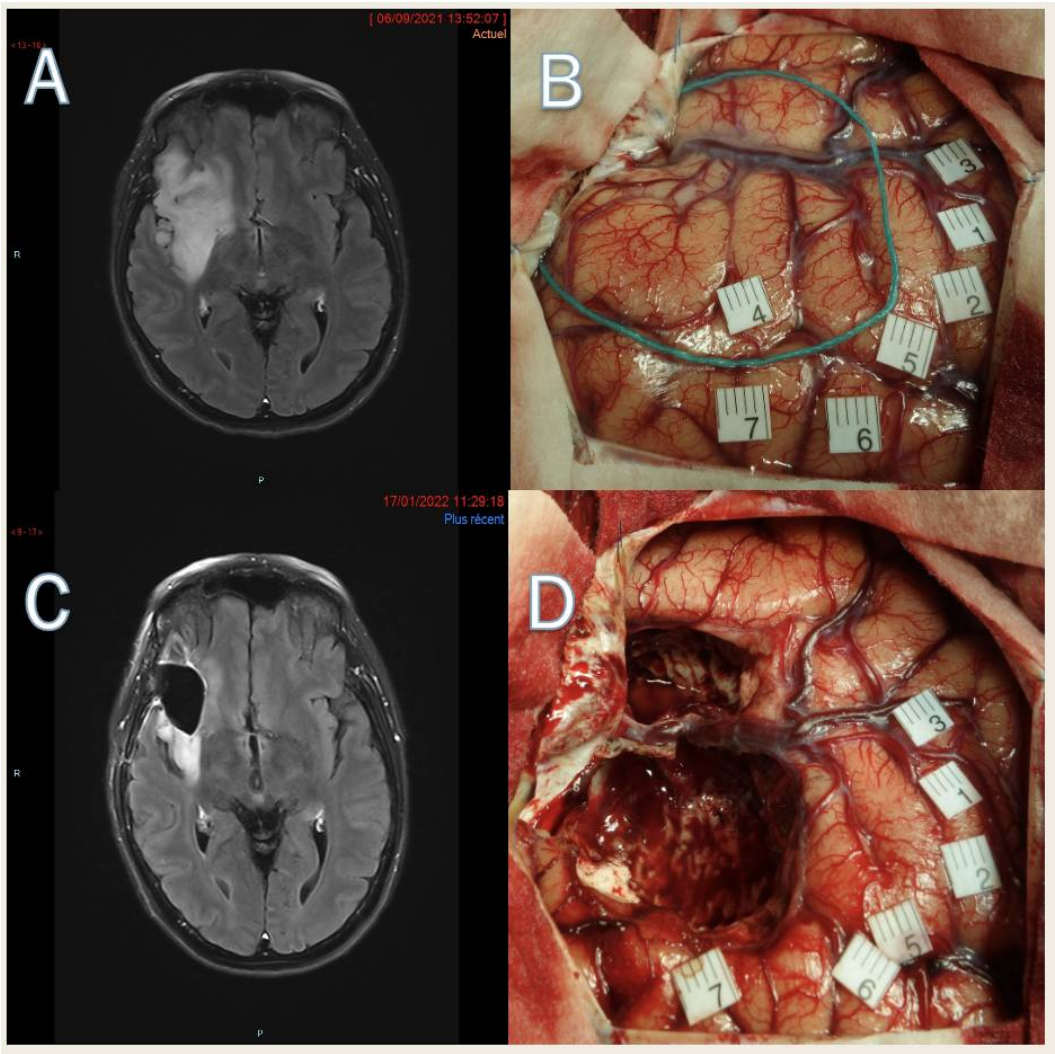


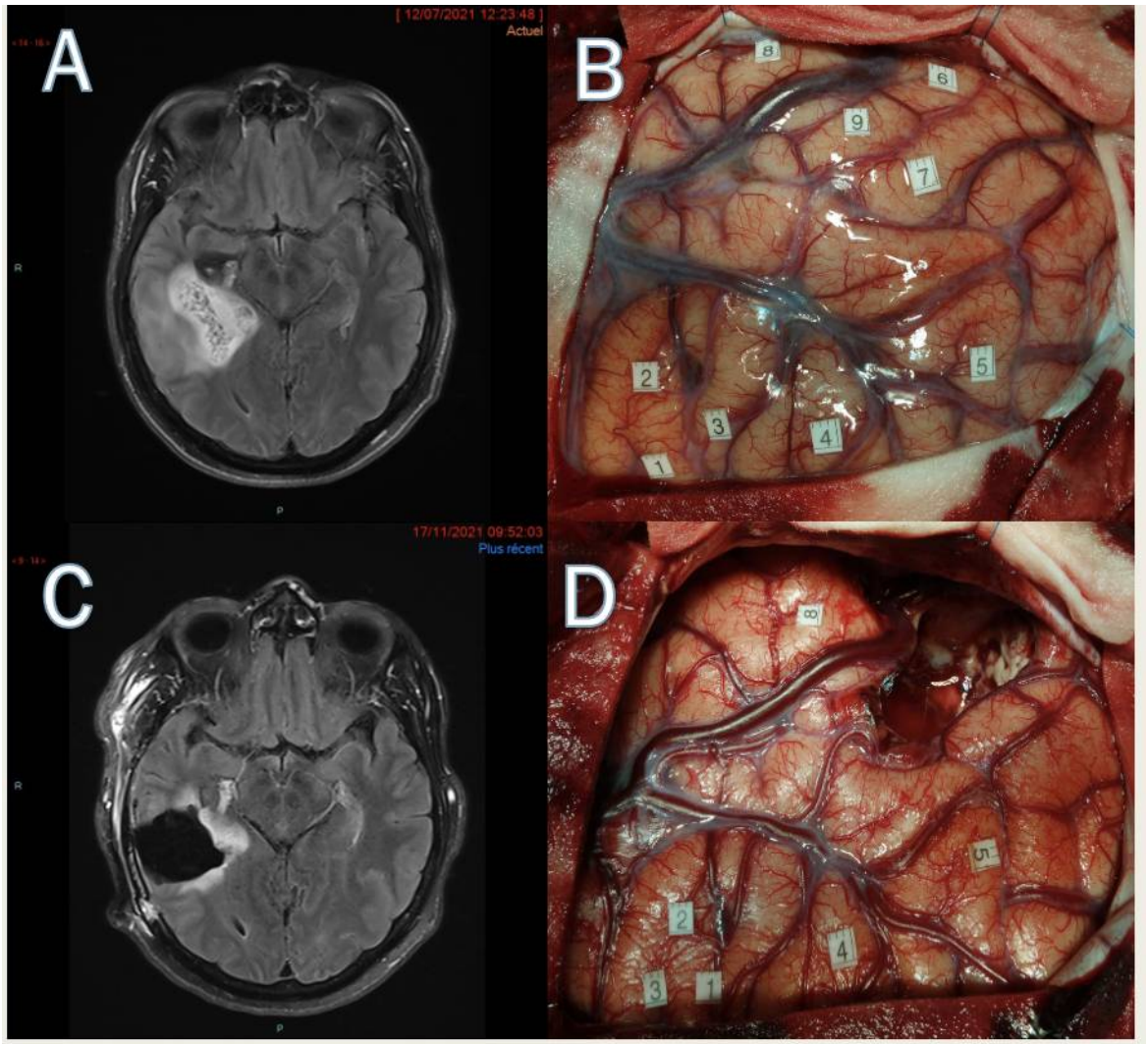
Figure 14: Kaplan Meier survival curve disaggregated by High Extent of resection.

After multivariable analysis, none of the variables showing clinically significant differences in the mean survival period had a P-value <0.05.

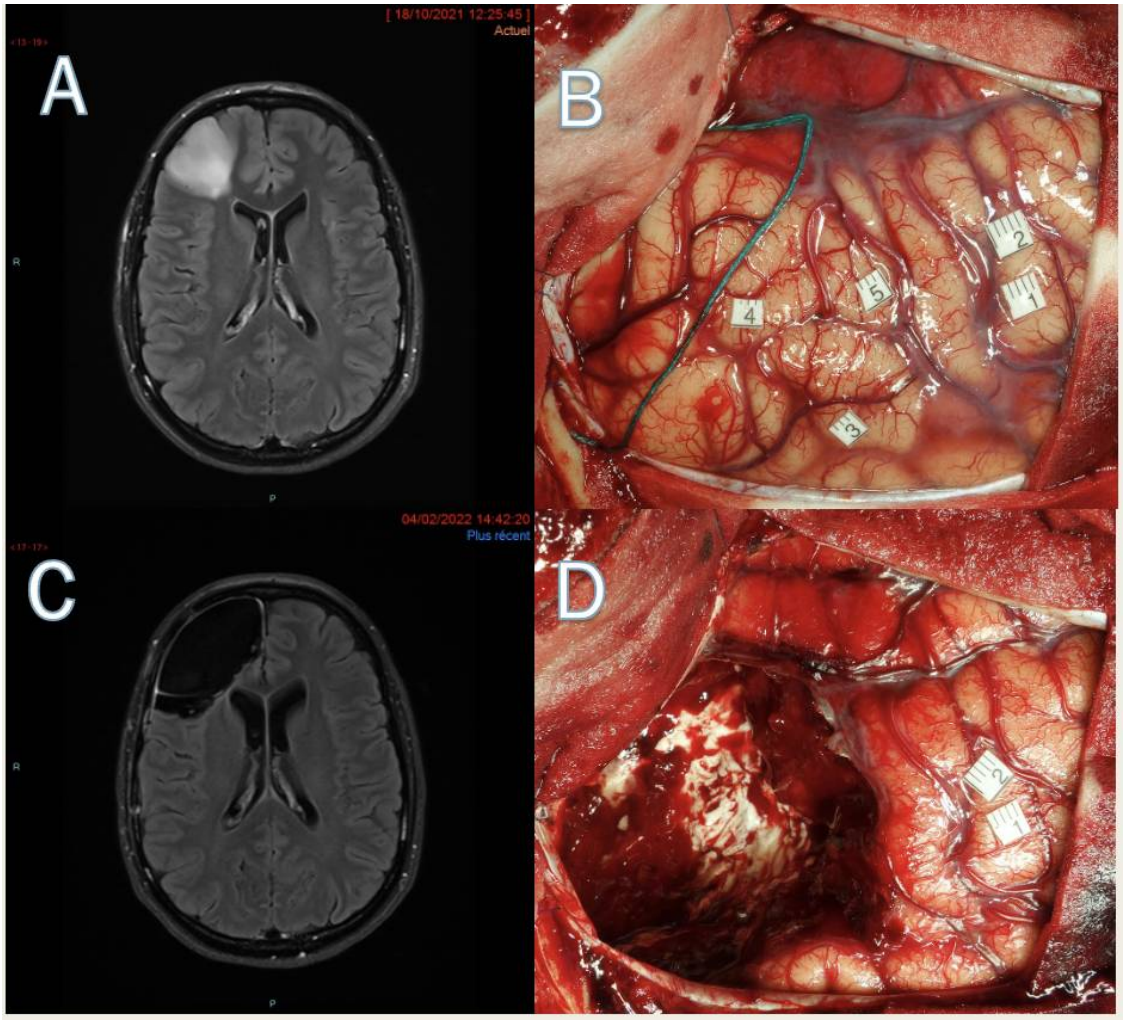
Part VI: Illustrative Cases



Case 1. Illustration of awake surgery for a right **t**emporo-insular Oligodendroglioma Grade III, IDH+1p19q+ which received radiotherapy after surgery. Preoperative magnetic resonance image (MRI; A) shows a right superior temporal gyrus tumor, which appears in hyper signal on the fluid-attenuated inversion-recovery sequence. Preresection photograph (B) shows cortical boundaries of the tumor (white labels) and areas of simulation, 4 months Postoperative MRI (C) and postresection photograph (D) show a subtotal resection of the tumor.



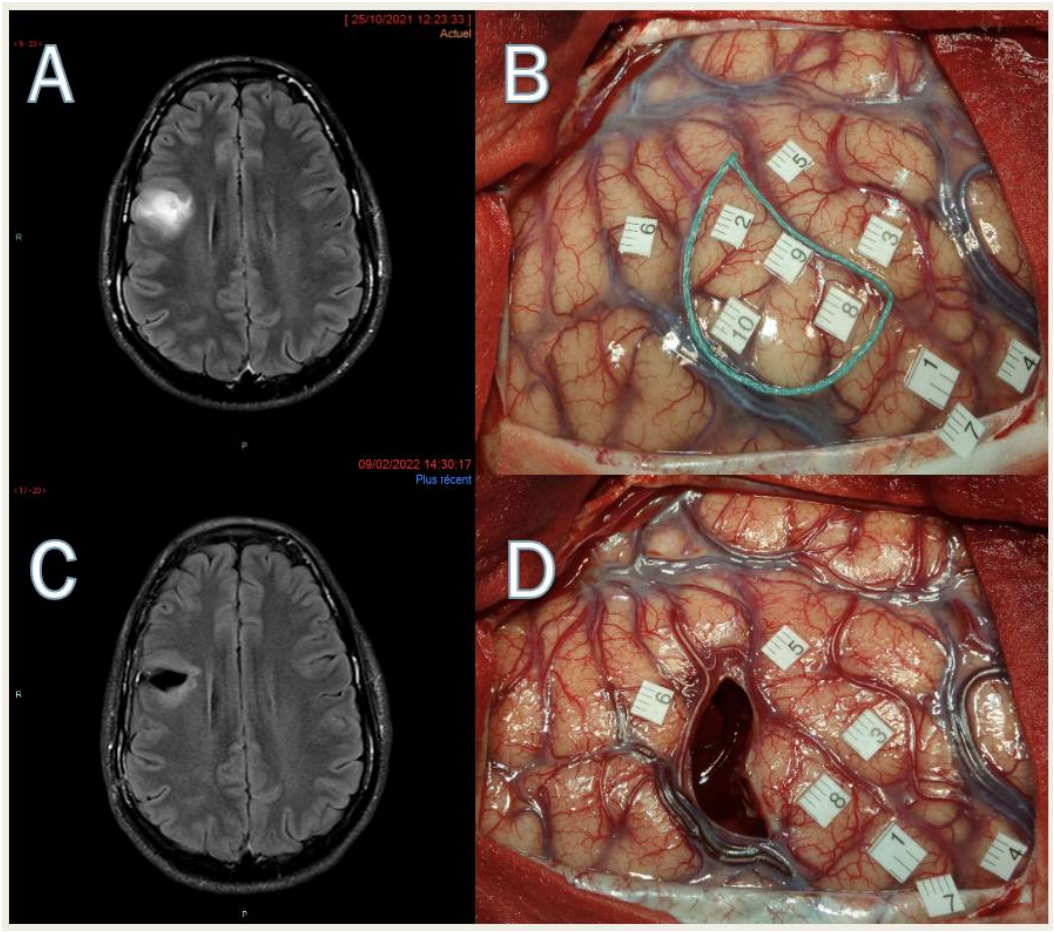
Case 2. Illustration of awake surgery for a right **t**emporal Astrocytoma Grade II, IDH+. Preoperative magnetic resonance image (MRI; A) shows a right inferior temporal gyrus tumor, which appears in hyper signal on the fluid-attenuated inversion-recovery sequence. Preresection photograph (B) shows cortical boundaries of the tumor (white labels) and areas of simulation, 3 months Postoperative MRI (C) and postresection photograph (D) show a subtotal resection of the tumor.



Case 3. Illustration of awake surgery for a right frontal Oligodendroglioma Grade II, IDH+1p19q+.Preoperative magnetic resonance image (MRI; A) shows a right superior Frontal gyrus tumor, which appears in hyper signal on the fluid-attenuated inversion-recovery sequence. Preresection photograph (B) shows cortical boundaries of the tumor (white labels) and areas of simulation, 3 months Postoperative MRI (C) and postresection photograph (D) show a GTR of the tumor.

Table 3: Case 3 per-procedure mapping stimulation records

number	**intensity in mA**	**errors**	**tests used for case 3**
1	1.5	Mouth deviation to the right	motricity face and hand
2	1.5	Mouth deviation to the right	
	1.5	No answer	Denomination: DO 80
3	1.5	Unconfirmed latency	Visual semantic pairings PPTT
4	1.5	Lack of certainty, unconfirmed	Social cognition: RMIE test



Case 4. Illustration of awake surgery for a right frontal Oligodendroglioma Grade II, IDH+1p19q+.Preoperative magnetic resonance image (MRI; A) shows a right pre-rolandic Frontal gyrus tumor, which appears in hyper signal on the fluid-attenuated inversion-recovery sequence. Preresection photograph (B) shows cortical boundaries of the tumor (white labels) and areas of simulation, 3 months Postoperative MRI (C) and postresection photograph (D) show a subtotal resection of the tumor.

Table 4:. Case 4 per-procedure mapping stimulation records

Indice	Amperage	Errors	Test utilisé
1	2 mA	Arthritis Disturbance	Moteur
2		Unconfirmed left nasal and ocular paresthesias	
3		Left hemi-tongue paresthesias	
4		Left thumb paresthesias	
5		Left hemi-tongue paresthesias	
6		Nasal paresthesias and hypophonia	
7		Paresthesias and left eye closure	Denominatio n DO 80
8		Latency and Arthritis Disturbance	
9		Unconfirmed arthritis disorders	
10		Missing words not confirmed	

End of mapping: semantic matching tests and Reading the mind in the eyes = no disturbance

End of excision:

Arthric slowing hypophonia and vocal hoarseness to arcuate bundle stimulation

Clones of the jaw on the left during the stimulation of the index 9

Final Test:

Properly performed bucco-facial praxis, slight dissymmetry when smiling on the left (possible link with clones)

Clear voice, Preservation of articulation, Absence of paresthesias of the hemiface Naming tests, and motor tests performed without disturbance.

Part VII: Discussion

Our study is one of a small number of publications on this topic. A small number of neuro-oncology centers practice hypnosedation due to the scarcity of the anesthetic skills and experience needed to perform hypnotherapy safely. Also, the evolution of the Annual volume of low-grade glioma surgery by the type of sedation showed the evolution of hypnosedation practice was correlated with the availability of only one Anesthesiologist who has the skills and experience to perform hypnosedation. we did not find evidence of a difference in the residual tumor volume between the two groups (32.14% of hypnosis-aided surgery tumors were <3mL vs. 48.78% for standard AAA surgery, OR=0.5, 95% CI=0.18-1.35, P= 0.17). However, patients with preoperative LGG volumes ≤ 20 mL were significantly longer (95% of patients with preoperative volumes ≤ 20 mL reach 5 years and 10 years OS, vs. 92% and 65% of patients with LGG volume ≥ 20 mL). IDH+ 1p19q - and, IDH+1p19q+ patients had a long overall survival than IDH- patients (100% and 82% of the IDH+1p19q-patients reach respectively 5years and 10 years OS , 92% and, 82% of IDH+1p19q+ patients versus 74% in IDH- patients).

Asleep-Awake-Asleep (AAA) vs Hypnosis:

A lot of previous studies on LGG reported that awake surgery offers the best compromise between the extent of resection and neurological cognitive preservation, i.e. the better onco-functional balance between impact on survival prognosis and quality-of-life **[44, 45, 46, 47].** Recent studies explored alternative techniques to the classical AAA for awake craniotomy, as the AAA technique might sometimes be challenging for anesthesiologists. Our team proposed a method based on hypnosis and sedation without orotracheal intubation or

laryngeal mask and showed that hypnosis was an effective and safe method for awake craniotomy **[6]**. Nonetheless, in this preliminary work, we did not assess the possible impact of hypnosis on oncological results.

Although we found in our series that the median OS of patients that had undergone AAA was better than patients of the hypnosis group (93% and 88% of patients in the AAA surgery group reach respectively 5years and 10 years OS versus 92% and 72% in hypnosis cohort, P=0.44) , we also found that the preoperative tumor volume was significantly higher in the hypnosis group than in the AAA group, i.e. 18/28 (64.28%) vs. 17/41 (41.46%) (P value=0.035). Yet, it has already been demonstrated that a preoperative larger tumor size is a negative prognostic factor of LGG **[48].** Thus, we believe that the difference in OS obtained between AAA and hypnosis might be related to the preoperative volume rather than a direct negative impact of hypnosis on the oncological outcome.

Regarding the residual tumor volume, one should have the same consideration about the possible impact of preoperative tumor volume. Indeed, even though only 9/28 (32.14%) of hypnosis cases had a residual tumor inferior to 3 cc, vs 20/41(48.78%) of AAA cases (P value= 0.17, Odd Ratio = 0.5 [0.18-1.35]), we believe this result is a direct consequence of higher preoperative tumor volume in the hypnosis group.

The only other study about hypnosis for awake craniotomy **[6]** had demonstrated the reliability of hypnosis as an original alternative method for performing a craniotomy. The authors reported that hypnosis does not suffer from the management of airways or the potentially long waking period, so that

allows going ahead with the two limitations of the AAA method, and suggesting that hypnosis could be an interesting alternative option for awake surgery of older populations **[6].** We believe that our results do not contradict these considerations, but should nevertheless lead to consider carefully hypnosis as a non-fully validated method that must be used only in research protocols.

Tumor Volume

In a previous study, Duffau reported that when no signal abnormality was visible on control MRI (complete resection), patients had a significantly longer OS compared with patients having any residual abnormality **[44].** It has also been demonstrated that tumor resection is associated with a better outcome than a biopsy **[49]**.

In our study, we used Mricron to convert neuroimaging files from DICOM to NIFTI and identify preoperative and postoperative tumors (6 months after surgery) on MRI 3D-T2 FLAIR sequence. We then calculated the preoperative and postoperative tumor volumes and the extent of resection using ITKSNAP 3D Segmentation. That allowed us to accurately measure the preoperative and postoperative tumor volume. Then we determined the extent-of resection (EOR) and stratified this data between the high extent of resection ≥95% or lower extent of resection <95%. The preoperative volume was stratified as ≤ 20 cc, between 20-40 cc or >40 cc. In another series of 190 DLGGs, Ius et al. showed that patients with an EOR ≥ 90% had an estimated 5-year OS of 93%, those with EOR between 70% and 89% had a 5-year OS of 84%, and those with EOR < 70% had a 5-year OS of 41% ($p<0.001$) **[45].** In our series, the 5 years and 10 years OS was significantly higher in the high extent of resection group (100%

and 87% of patients with an EOR ≥95% reached respectively 5years and 10 years versus 89% and 78% of patients with an extent resection < 95%). Multiple similar data have already been reported, demonstrating the impact of preoperative tumor volume and of EOR on survival in LGG **[46,47]**. Our results confirm these already well-known prognostic factors, whatever the surgical method used for resection.

Molecular profile

Maximilian J. Mair et al. **[50],** reported in 2020 in a review that the prognosis of anaplastic astrocytoma patients without IDH mutation is significantly worse (median OS 19.4 - 20 months) compared to anaplastic astrocytoma with IDH mutation (median OS 65 – 81.1 months) **[51, 52].** In our series, the 10 years OS was reached in 82% of IDH+ patients versus 74% of IDH- patients.

Limitations

The main goal of our study was to assess the impact of hypnosis on oncological results of surgical resection of LGG. To better interpret our results, we collected the maximum of clinical, radiological, and molecular data, to try and confirm that this retrospective study did not suffer too many methodological biases.

The main limitations we identified are the retrospective collection of data, and the small sample of patients in each group as only 41 AAA vs 28 Hypnosis cases was studied.

Nonetheless, one should consider that all the patients have been treated by the same neurosurgical and neuro-oncological team, whatever the anesthetic method is chosen (hypnosis or AAA), which may have limited the heterogeneity of the groups and the impact of surgical technique or oncological treatments, such as chemotherapy or radiotherapy, on OS.

Besides, we did not find any other study in the literature about hypnosis for LGG to compare our results. This hypnosis method is indeed not yet widespread due to the low probability to have the opportunity to work in an institution with neuro-anesthesiologists both involved in awake surgery and in hypnosis.

Conclusion

This study did not demonstrate the superiority of one method over the other, but hypnosis should still be considered as a non-fully validated method for awake craniotomy and we encourage neurosurgical teams to use this method under research protocols to obtain robust data that may help anesthesiologists to propose hypnosis in adequate situations, such as in patients with comorbidities that could contraindicate the classical AAA procedure. Hypnosedation is a suitable alternative to standard sedation in awake craniotomy for LGGs; however, it does not lead to greater resection or longer overall survival. Tumor volumes and extent of resection remain better determinants of overall survival in LGGs, and patients with less favorable volumetrics tend to be hypnosedated.

Abstract

Title: Awake versus Hypnosis for Low-grade Gliomla Surgery: Long term Follow-up Results

Author: Dr Nourou Dine Adeniran Bankole

Keywords: Low-grade Glioma, Awake craniotomy, Hypnosis, overall Survival,IDH mutations

Background:

Hypnosis-aided craniotomy is a safe alternative to standard asleep-awake-asleep (AAA) surgery in glioma surgery. Its principal indication remains contraindications to general anesthesia.

Objective:

This study aimed to evaluate the association between the choice of sedation (i.e., hypnosedation vs. standard sedation) and postoperative outcomes in awake low-grade glioma surgery.

Methods:

LGG patients who underwent awake surgery between May 2011 and December 2019 at the authors' institution were included in the analysis. Pearson Chi-square, Fisher exact, and Mann-Whitney U tests were used for inferential analyses, and a P-value <0.05 was considered statistically significant. Also, stratified Kaplan Meier curves were used to visualize survival.

Results:

Sixty-nine (69) patients were included, thirty-six were male (52.2 %), and the mean age was 40.8 (+/-12.06) years. Most patients had IDH+ tumors (79.71%), 35 patients (50.72%) had a preoperative tumor volume >40 mL and 40 (57.97%) had postoperative tumor volume ≥ 3cc. Twenty-eight patients (40.58%) were hypnosedated while 41 (59.42%) received standard anesthesia. Both techniques had the same results in terms of subtotal (≥95%) extent of resection (10.15% vs. 11.59%, P=0.51) or overall survival (23.78 years 95% CI=20.72-26.83 years vs. 12.50 years, 95% CI=19.85-25.53 years).

Conclusion: Hypnosis for awake craniotomy is still less used although it is a suitable alternative to standard sedation in awake craniotomy for LGGs; however, it does not lead to greater resection or longer overall survival.

Résumé

Titre: Chirurgie éveillée standard versus hypnose pour la chirurgie du Gliome de bas grade: Résultats de suivi à long terme

Auteur: Dr Nourou Dine Adeniran Bankole

Mots-clés: Gliome de bas grade, Craniotomie éveillée, Hypnose, Survie globale, Mutations IDH.

Introduction

La craniotomie assistée par hypnose est une alternative sûre à la chirurgie standard endormi-éveillé-endormi (AAA) dans la chirurgie du gliome. Son indication principale reste les contre-indications à l'anesthésie générale.

Objectifs:

Cette étude visait à évaluer l'association entre le choix de la sédation (c'est-à-dire l'hypnosédation par rapport à la sédation standard) et les résultats postopératoires dans la chirurgie éveillée du gliome de bas grade.

Méthodes:

Les patients avec un gliome de bas grade qui ont subi une chirurgie éveillée entre mai 2011 et décembre 2019 dans notre institution ont été inclus dans l'analyse. Les analyses uni variées et multivariées ont été utilisées .Une valeur P<0,05 a été considérée comme statistiquement significative

Résultats:

Soixante-neuf (69) patients ont été inclus, trente-six étaient de sexe masculin (52,2%), et l'âge moyen était de 40,8 (+/-12,06) ans. La plupart des patients avaient des tumeurs IDH+(79,71 %), 35 patients (50,72%) avaient un volume tumoral préopératoire>40 mL et 40 (57,97 %) avaient un volume tumoral postopératoire ≥3 cc. Vingt-huit patients (40,58%) ont été hypnosédatés tandis que 41(59,42 %) ont reçu une anesthésie standard. Les deux techniques ont eu les mêmes résultats en termes d'extension d'exérèse tumorale (≥95 %) (10,15 % contre 11,59%, P=0,51) ou de survie globale (23,78ans IC à 95 % = 20,72-26,83 ans contre 12,50 ans, 95 % IC=19,85-25,53 ans).

Conclusion:

L'hypnose pour la craniotomie éveillée est encore moins utilisée bien qu'elle soit une alternative appropriée à la sédation standard dans la craniotomie éveillée pour les LGG ; cependant, cela ne conduit pas à une résection plus importante ou à une survie globale plus longue.

ملخص

العنوان: جراحة اليقظة القياسية مقابل التنويم المغناطيسي لجراحة الورم الدبقي منخفضة الدرجة: نتائج المتابعة طويلة المدى

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الكلمات الأساسية: الورم الدبقي منخفض الدرجة، حج القحف المستيقظ، التنويم المغناطيسي، البقاء على قيد الحياة بشكل عام، طفرات IDH.

مقدمة:

حج القحف بمساعدة التنويم المغناطيسي هو بديل آمن للجراحة القياسية للنوم واليقظة والنوم (AAA) في جراحة الورم الدبقي. يبقى المؤشر الرئيسي له موانع للتخدير العام.

الأهداف:

هدفت هذه الدراسة إلى تقييم العلاقة بين اختيار التخدير (أي التنويم المغناطيسي مقابل التخدير القياسي) ونتائج ما بعد الجراحة في جراحة الورم الدبقي منخفضة الدرجة.

أساليب:

تم تضمين المرضى الذين يعانون من الورم الدبقي منخفض الدرجة والذين خضعوا لعملية جراحية أثناء اليقظة بين مايو 2011 وديسمبر 2019 في مؤسستنا في التحليل. تم استخدام اختبارات Pearson Chi-square و Fisher دقيقة و Mann-Whitney U للتحليلات الاستنتاجية ، واعتبرت قيمة P <0.05 ذات دلالة إحصائية. بالإضافة إلى ذلك ، تم استخدام منحنيات كابلان ماير الطبقية لتصور البقاء على قيد الحياة.

نتائج:

تم اشتمال تسعة وستين (69) مريضا، ستة وثلاثون من الذكور (52.2٪)، وكان متوسط العمر 40.8 (+/-12.06) سنة. كان لدى معظم المرضى أورام (79.71٪) + IDH)، وكان لدى 35 مريضًا (50.72٪) حجم ورم قبل الجراحة>40 مل و 40 (57.97 ٪) كان حجم الورم بعد الجراحة ≤3 سم مكعب. ثمانية وعشرون مريضا (40.58٪) تم تنويمهم بينما تلقى 41 (59.42٪) تخدير معياري. كان للطريقتين نفس النتائج من حيث تمديد استئصال الورم (95٪≤) (10.15٪ مقابل 11.59٪ ، P = 0.51) أو البقاء الإجمالي (23.78 سنة IC إلى 95٪=20.72-26.83 سنة مقابل 12.50 سنة ، 95٪ CI = 19.85-25.53 سنة).

الخلاصة:

التنويم المغناطيسي لحجر القحف اليقظ يستخدم بشكل أقل على الرغم من أنه بديل مناسب للتخدير القياسي في حج القحف اليقظ لـ LGG ؛ ومع ذلك ، فإن هذا لا يؤدي إلى استئصال أكبر أو البقاء على قيد الحياة لفترة أطول.

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