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Clinical study

Glioma surgery: From preservation of motor skills to conservation of cognitive functions

Roberto Altieri [a,d,*], Simona Raimondo [b], Cristiana Tiddia [b], Diego Sammarco [b], Fabio Cofano [a], Pietro Zeppa [a], Matteo Monticelli [a], Antonio Melcarne [a], Carola Junemann [a], Francesco Zenga [a], Riccardo Savastano [c], Diego Garbossa [a], Francesco Certo [d,e], Giuseppe Barbagallo [d,e]

[a] *Neurosurgical Unit, Department of Neuroscience, University of Turin, Turin, Italy*
[b] *ENT Unit, Department of Surgery, University of Turin, Turin, Italy*
[c] *AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy*
[d] *Division of Neurosurgery, Department of Neurosciences, Policlinico "G.Rodolico" University Hospital, Catania, Italy*
[e] *Interdisciplinary Research Center on Brain Tumors Diagnosis and Treatment, University of Catania, Catania, Italy*

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A B S T R A C T

The first step of glioma treatment is surgery. Extent of resection (EOR) improves patient survival if surgery does not negatively impair a patient's neurological status. However, how surgery affects the patient's quality of life (QOL) has been less studied, especially as regards cognitive aspects. In our study, we retrospectively analyzed our cases with awake surgery. In all patients, surgical excision was stopped when active functions were intraoperatively identified. A neuropsychological assessment was performed both before and after surgery (5 days and 1 month after). Writing, motor speech, comprehension, expression, reading, pragmatics, attention, memory, problem solving and visuoperceptive functions were evaluated and scored with the NOMS scale. We found no differences in the median values of writing and motor speech, while there was a difference in the following variables: comprehension, expression, reading, pragmatics, attention, memory, problem solving and visuoperceptive functions. Moreover, the Dunn test did not show any difference between preoperative evaluation and evaluation performed 30 days after surgery regarding comprehension, expression, reading, pragmatics, attention, problem solving and visuoperceptive functions. However, there was a difference between preoperative and postoperative evaluation for memory. This retrospective study shows that awake surgery could be a reasonable possibility to preserve a patient's QOL achieving an EOR >82% of the Total Tumor Volume (Fluid-attenuated inversion recovery (FLAIR) hyperintense region in low-grade gliomas and enhancing nodules plus FLAIR hyperintense region in high-grade gliomas). In this series memory was the only aspect that had an impairment after surgery without a complete recovery at one month after surgery.

1. Introduction

Today the mainstay of glioma treatment remains surgery followed by the Stupp regimen in cases of Glioblastomas (GBM) [1–3]. For many years, clinicians focused their attention on overall survival (OS) and progression free survival (PFS) [4–7]. It is well demonstrated that extent of resection (EOR) improves patient survival if surgery does not negatively impair a patient's neurological status and it is generally evaluated with the Karnofsky Performance Status scale (KPS) [6,8,9]. This scale focuses especially on motor ability because the ability of patients to provide for their own care is the major concern to start the Stupp regimen [10–14]. However, how surgery affects the quality of life (QOL) has been less studied in these patients, especially as regards cognitive, affective and relational aspects. Recently, Duffau et al. investigated this concern for low-grade gliomas (LGG) and proposed a new surgical philosophy in which QOL was intended to be the first clinical target, and whose feasibility depends, above all, on surgical preservation of major cognitive functions, achievable with awake surgery [5,15–18]. It is related to a new concept of the brain: there are no eloquent areas because the whole brain is eloquent thanks to the connection of white matter fibers. From the "connectome" perspective, the only possibility to achieve a maximal safe resection is cortical and subcortical mapping with the patient's active cooperation.

* Corresponding author at: Neurosurgical Unit, Department of Neuroscience, University of Turin, via Cherasco, 15, 10126 Turin, Italy.
E-mail address: roberto.altieri.87@gmail.com (R. Altieri).

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In our study, we retrospectively analyzed our cases with awake surgery in order to investigate how surgery affects main cognitive domains.

2. Materials and methods

We retrospectively analyzed our surgical cases in awake surgery. Inclusion criteria were: age between 17 and 75 years, neuroradiological diagnosis of glioma involving the Rolandic area, insular region, and/or left temporal lobe. Exclusion criteria were: age <17 years and >75 years in order to avoid patients' lack of compliance during surgery (difficulty to remain calm and achieve concentration in the pediatric population and fatigue in the elderly); among the patients who met the initial age criteria we excluded those who were affected by gliomas in the "non-high functional" brain regions such as the right temporal lobe, occipital lobe, parietal lobe away from the Rolandic area, and right frontal lobe away from the Rolandic gyrus. All patients were treated with the aim of achieving the maximal safe resection, and surgical excision was stopped when active functions were intraoperatively identified with three consecutive responses at the same point during cortical/subcortical stimulation.

2.1. Surgical considerations

All patients were operated on by the same surgical team under local anesthesia with cortical and subcortical brain mapping achieved by direct electrical stimulation (DES). Brain mapping was carried out in every case by the first author. DES was performed using bipolar electrodes separated by a distance of 5 mm. Electrocorticography was performed on each patient with an initial stimulation intensity of 2.5 mA, then increasing up to a maximum of 10 mA; we found functional feedback responses in this range in all patients. The stimulation intensity was recorded for each patient's mapping procedure. We started with a double task (contralateral arm movement and counting) to identify the Negative Motor Network (NMN) around the inferior frontal gyrus (IFG) and sensorimotor area. When we evoked a total motor arrest (TMA), we followed the mapping with the same amplitude stimulus. Denomination test (DO80), Pyramid Palm Tree Test (PPT test) and Reading the Eyes in the Mind test (REM test) were administered to identify language and mentalizing responses [19]. We considered the point in which there were already 3 consecutive feedbacks after DES as positive. The labeled mapping sites were recorded by digital photography prior to and following tumor resection. Tumor resection was also guided with frameless navigational guidance based on the preoperative MRI. A postoperative MRI scan, within 48 h, was routinely performed. Tumor volumes were calculated with manual segmentation using Horos software for the Mac Os by two Neurosurgeons with expertise in the Neuro-Oncological field and experience with Neuroradiological imaging reconstruction. Enhancing Nodule (EN), FLAIR volume and Total Tumor Volume (TTV) were calculated in the pre- and post-operative MRIs. The EOR of ENs and TTV were then calculated.

2.2. Neuropsychological evaluation

A neuropsychological assessment before and after surgery (5 days and 1 month after) was performed by trained speech therapists. Writing, motor speech, comprehension, expression, reading, pragmatics, attention, memory, problem solving and visuoperceptive functions were evaluated according to a recent survey [20] and scored with the NOMS scale [21,22].

2.3. Patients

Between 1st January 2017 and 5th August 2018 we performed 23 awake surgeries. Thirteen (57%) patients were male and 10 (43%) female, the mean age was 48 years (range, 17–72 years); 43% of patients had a tumor located in the right hemisphere (group 1) and the remaining 57% had a tumor located in the left (group 2). In group 1 there were 2 fronto-temporo-insular tumors (20%), 3 frontal tumors near the Rolandic area (30%), 2 fronto-parietal tumors (20%), 1 fronto-insular tumor (10%), 1 parieto-insular tumor (10%), and 1 parietal tumor (10%). In group 2 there were 6 temporal tumors (47%), 1 fronto-temporo-insular tumor (7%), 5 frontal tumors (39%), and 1 parietal tumor (7%).

All patients underwent MRI after seizures; two patients developed a preoperative hemiparesis (Table 1). Pathological findings showed a DNET in 4%, Grade II Astrocytomas (IDH1 mutated, 1p19q non-codeleted) in 17%, Grade II Oligodendroglioma (IDH1 mutated, 1p19q codeleted) in 27%, Anaplastic Astrocytoma in 13%, and Glioblastomas in 39%.

2.4. Statistical analyses

The statistical analyses were performed using STATA v12 software. The Kruskal Wallis test was carried out to compare the median value of every domain at three different sampling times (before surgery, 5 days and 1 month after surgery). The Dunn test was then performed as a post-estimation test for multiple pairwise comparisons. We then repeated the same analyses on groups 1 and 2. Furthermore, we repeated these same tests dividing the entire cohort into two other groups (high-grade glioma (HGG group) and low-grade glioma (LGG group) according to the pathological diagnosis.

3. Results

We achieved an EOR of 100% for ENs in every enhancing tumor. Overall, the median preoperative TTV (FLAIR hyperintense region in LGG and ENs plus FLAIR hyperintense region in HGG) was 30.25 cc (range, 9.8–199.34). The median postoperative TTV was 3.2 cc (range, 0–40.25 cc). The median EOR of TTV was 82.42% (range, 12.60%–100%). No additional motor deficits were observed after surgery.

The Kruskal Wallis test showed no differences at the three sampling times in the median values of writing and motor speech, while there was a difference in the medians for the following variables: comprehension, expression, reading, pragmatics, attention, memory, problem solving and visuoperceptive functions (Table 2). Moreover, the Dunn test showed a significant difference between preoperative evaluation and evaluation at the 5th postoperative day, however, there was no difference between preoperative evaluation and evaluation performed 30 days after surgery regarding comprehension, expression, reading, pragmatics, attention, problem solving and visuoperceptive functions. A difference between preoperative and postoperative evaluation was found, however, there was no difference between the evaluation performed 5 days and 30 days after surgery for memory.

The same analyses were carried out separately for tumors located in the right and left hemisphere. In the right hemisphere the Kruskal Wallis test showed a significant difference only for attention (pV 0.02) and visuoperceptive functions (pV 0.04), while the Dunn test showed a significant difference between preoperative evaluation and evaluation at the 5th postoperative day, however, there was no significant difference between preoperative evaluation and the evaluation performed 30 days after surgery (Fig. 1).

Table 1
Patients' clinical and intraoperative data. PrecG (Precentral Gyrus); PostcG (Postcentral Gyrus); SMA (Supplementary Motor Areas); OpG (Opercular Gyrus); SMG (Sensory-Motor Gyrus); AG (Angular Gyrus); SM (Supramarginal Gyrus); CR (Corona Radiata); IFOF (Inferior Fronto-Occipital Fascicle).

Male	Female	Right Hemisphere	Left Hemisphere	Preoperative seizures	Intraoperative seizures	Intraoperative responses at DES	Mean Positive DES responses at	Preoperative focal deficit	New postoperative focal deficit
57%	43%	43%	57%	100%	0	-TMA at PrecG; SMA; SMG; PostcG; dysarthria at PrecG; -Contraction at CR -Speech arrest at SMG; OpG; - Phonological and semantic paraphasias at IFOF; AG; SM -Anomia at AG	5.5 mA	Hemiparesis in 9% of patients	No

Table 2
Comparison of median values of every task using the Kruskal Wallis test. There is no statistical significance for writing and motor speech.

	Preop	5 days after surgery	30 days after surgery	p value Kruskal Wallis
Comprehension	7	6	7	0.01
Expression	7	6	7	0.01
Reading	7	6	7	0.04
Writing	7	7	7	0.28
Pragmatics	7	6	7	0.03
Motor speech	7	7	7	0.07
Attention	7	6	7	0.005
Memory	7	6	6	0.01
Problem solving	7	6	7	0.04
Visuoperceptive function	7	6	7	0.02

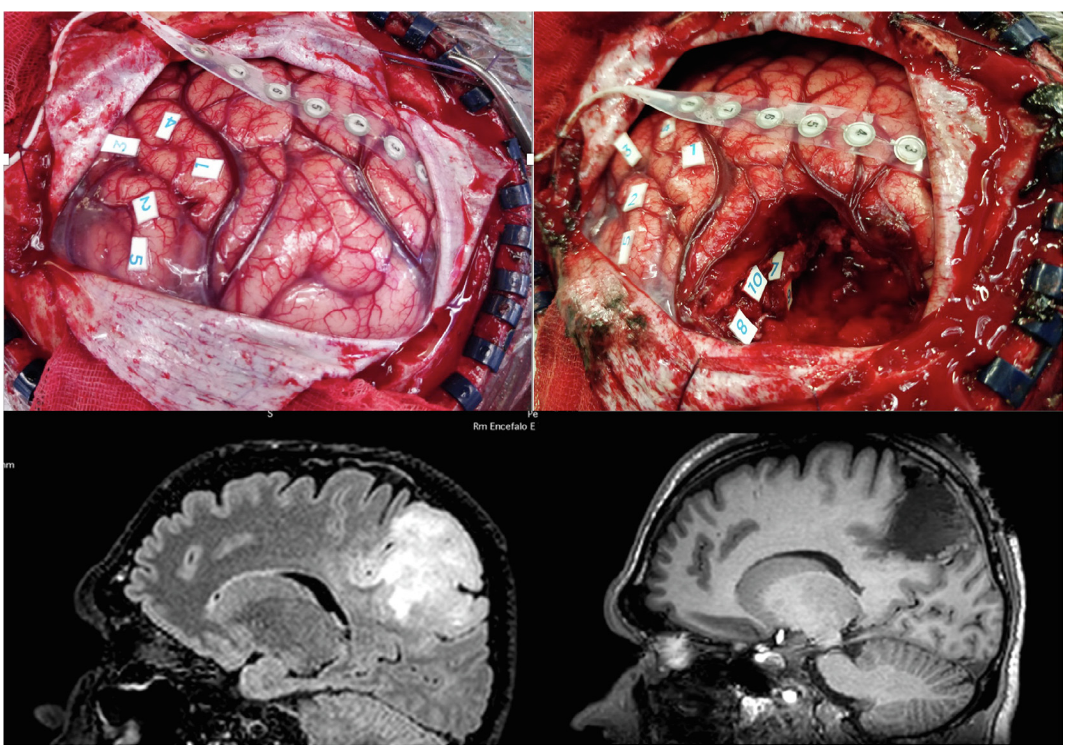

Fig. 1. Cortical mapping of a right parietal LGG with a detailed labeling of the primary motor network (1, 4) found thanks to the involuntary contraction of the contralateral arm at DES. The other numbers (5, 2, 3) mark the NMN that was identified for TMA at DES (A); a cortical and subcortical mapping at the end of resection showing the cortico-spinal tract (7, 8, 9, 10) (B). In (C) we can see a preoperative MRI and in (D) there are the postoperative results of surgery.

In the left hemisphere, the Kruskal Wallis test showed a significant difference only for comprehension (pV 0.04), expression (pV 0.02), reading (pV 0.04), attention (pV 0.02) and memory (pValue 0.04). The Dunn test showed that there was a significant difference between preoperative evaluation and the evaluation at the 5th postoperative day but no difference between preoperative evaluation and the evaluation performed 30 days after surgery for comprehension, expression, reading and attention. Results confirmed

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differences between preoperative and postoperative evaluation but not between the evaluation performed 5 days and 30 days after surgery for memory. Furthermore, data from group 2 showed a strong difference between preoperative evaluation and the evaluation at the 5th postoperative day for the expression value but no difference between preoperative evaluation and the evaluation carried out after one month (Fig. 2).

In the HGG group the Kruskal Wallis test showed no differences at the three sampling times in the median values of writing, while there was a difference in the median values for the following variables: comprehension, expression, reading, pragmatics, motor speech, attention, memory, problem solving and visuoperceptive functions. The Dunn test showed a significant difference between preoperative evaluation and the evaluation at the 5th postoperative day, but there was no difference between preoperative evaluation and the evaluation performed 30 days after surgery regarding all of these domains except for memory that, instead, remained impaired at the second follow-up after surgery (30 days).

In the LGG group the Kruskal Wallis test showed no differences at the three sampling times in the median values of reading, writing, pragmatics, motor speech, memory and problem solving, while there was a differences in the median values for the following variables: comprehension, expression, attention and visuoperceptive functions. In all of these domains, the Dunn test showed a significant difference between preoperative evaluation and the evaluation at the 5th postoperative day, but there was no difference between preoperative evaluation and the evaluation performed 30 days after surgery.

4. Discussion

The results of our surgical series seem to suggest that awake surgery gives the possibility to achieve a safe supratotal resection of ENs in HGG and an EOR of >80% of TTV in LGG and HGG. Surgery affects different components of the human cognitive sphere. In our cases, there were no patients in whom there was an impairment in writing and motor speech capacity. Generally, a slight early postoperative impairment in comprehension, expression, reading, pragmatics, attention, memory, problem solving and visuoperceptive functions was registered with a complete recovery for all of these except memory. After stratifying the patients into two groups based on tumor side (groups 1 and 2), a slight early postoperative impairment only for attention and visuoperceptive functions was noted in the right hemisphere, suggesting its preeminent role in these functions. However, in the left hemisphere there was an involvement of comprehension, expression, reading,

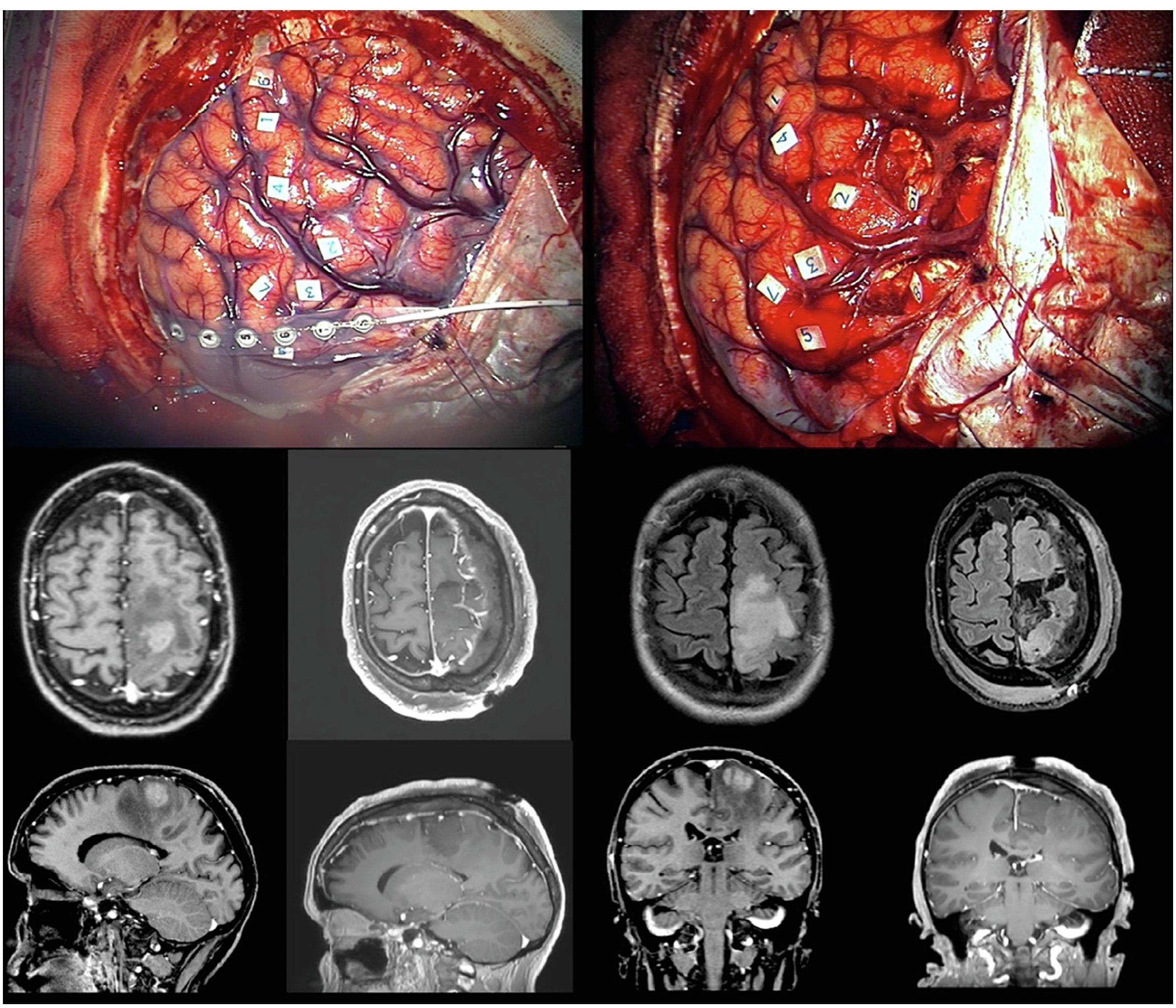

Fig. 2. The images show brain mapping of a left frontal Glioblastoma, involving the primary motor areas and the supplementary motor areas, before and after resection. The cortical numbers delimited the NMN while the subcortical numbers identified the corona radiata found thanks to the contraction of contralateral arm and leg at DES; at the bottom, we can see the preoperative MRI and the Neuroradiological result after excision with the complete resection of the EN and the FLAIR residual tumor in the prerolandic gyrus.

attention, and memory, with a prevalent role for expression, underlying its role in communication. In this series, memory was the only aspect that had an impairment after surgery without a complete recovery at one month after surgery. Moreover, after stratifying the patients into two groups based on pathological diagnosis (HGG and LGG groups), we observed a slight early postoperative impairment in all domains except for writing. All patients had a complete recovery of all functions at 30 days after surgery, except for memory. In the LGG group, instead, we found a slight early postoperative impairment only for comprehension, expression, attention and visuoperceptive functions with a complete recovery at the second follow-up. Therefore, we can suppose that surgery impairs neuropsychological domains more in the HGG then in the LGG group, also at an early stage, and that this could be due to the slow growth of LGG giving more time for brain neuroplasticity. This data should be evaluated in a long-term follow-up and, if confirmed, a specific intraoperative task for memory should be developed to preserve this crucial aspect of human cognition especially in HGG surgery.

Nowadays, it is well known that glioma surgery is the first action to be taken in the treatment of these tumors and the aim of this practice is to maximize tumor excision while preserving brain function [2,5,9,23,24]. This kind of surgery, performed in specialized centers, results in a permanent neurological impairment in about 7% of cases, with particular regard to motor and language function. This morbidity could be lowered to 3.4% if brain mapping is performed [25]. Cognitive functions are also involved in these patients due to tumor infiltration, edema, seizures, and drugs but this aspect has been less studied [26].

It is also well known that brain functions related to a correct interpretation of and an adequate interaction with reality are distributed in a wide neural network [27]. It is accepted that the "primary cognitive cortex" is formed of the infero-lateral prefrontal areas, temporoparietal junction, cingulum and precuneus with some degree of right hemisphere dominance [5,18,28]. Moreover, in these areas mirror neurons have been described that subserve for intuitive understanding of another person's affective or intentional states, and reflective inferences, such as the attribution of complex distal intentions or motives. Neurocognitive impairment could be caused by damage to cortical areas and by the disconnection of these with an interruption of the superior longitudinal fascicle, arcuate fascicle and inferior fronto-occipital fascicle [19,20,28]. Another crucial structure is the default mode network involving the cingulum. It is involved in attention and motivation, and, when damaged, could result in the abulic syndrome [29]. Therefore, in the light of these new data, awake surgery should be not considered only an alternative technique but a necessary tool in Neuro-oncological surgery [30]. For many years, the "dogma" of right non-dominant hemisphere resulted in the selection of the awake procedure with language mapping only for lesions located in the left side. However, postoperative neuropsychological assessments performed in patients affected by right-side tumors frequently showed cognitive and behavioral deficits. Therefore, to preserve QOL, awake surgery with cortical and subcortical mapping has recently been proposed for the resection of right-hemisphere tumors. Duffau et al., using mapping in awake patients also affected by right-side tumors, demonstrated a right hemisphere role in movement execution and control, visual processes and spatial cognition, language and nonverbal semantic processing, executive functions (e.g., attention), and social cognition (mentalizing and emotion recognition) [30]. Hendriks et al. in a recent paper, analyzed retrospectively 59 patients treated for gliomas. They showed that a cognitive improvement in any single domain occurred in 17%, cognitive impairment in any single domain in 42%, and decline in more than one domain in 17% of patients. The most frequently affected aspects were attention and information processing. Resection regions associated with decline in more than one domain were predominantly located in the right hemisphere. For attention decline, no specific region could be identified. For decline in elaboration speed, several regions were found, including the frontal pole and the corpus callosum. Cognitive decline after resective surgery of diffuse glioma was prevalent, in particular, in patients with a tumor located in the right hemisphere without cognitive function mapping [28].

This is a retrospective study of a small cohort of patients with a limited follow-up. Further analyses should be carried out on a larger series with a complete Neuro-Oncological and Neurophysiological follow-up to confirm our preliminary results.

5. Conclusion

This retrospective study shows that awake surgery could be a reasonable possibility to preserve a patient's cognitive status achieving a satisfactory EOR. Our patients did not experience any decline in motor speech and writing function, they benefited from a complete recovery of comprehension, expression, reading, pragmatics, attention, problem solving and visuoperceptive functions after 30 days. Intraoperative specific tasks for attention and visuoperceptive functions should be made for patient with tumors in the right hemisphere, while dedicated tasks could be performed for comprehension, expression, reading, attention and memory in patients affected by a tumor located in the left hemisphere. Special attention in this latter group should be reserved especially for expression and memory. Memory is, indeed, the only cognitive function with a permanent decline after 30 days. Further studies are needed to investigate the possibility of a later recovery. Data also suggest that surgery impairs neuropsychological domains more in the HGG surgery then in the LGG surgery supporting the evidence of better brain neuroplasticity in the latter group. However, awake surgery is not considered the gold standard for patients affected by HGG, we believe that in selected cases it could be considered a useful tool for patients with a short survival expectancy because it is crucial to preserve both motor and cognitive function integrity, especially if surgery cannot significantly increase the prognosis *quoad vitam*.

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Compliance with ethical standards

- *Disclosure of potential conflicts of interest:* on behalf of all authors, the corresponding author states that there is no conflict of interest.
- *Funding:* no funding was received.
- *Ethical approval:* all procedures performed for this study were in accordance with the ethical standards of Azienda Ospedaliera Universitaria Città della Salute e della Scienza of Turin and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
- *Informed consent:* for this type of study formal consent is not required.

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