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SHORT REVIEW

Is non-awake surgery for supratentorial adult low-grade glioma treatment still feasible?

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Abstract In this short review, the author performs a database search, summarizes, and discusses studies that provide information on the need to perform awake surgery to preserve quality of life/return to work of adult patients who undergo resection for a supratentorial low-grade glioma (LGG). Based upon the currently available data, the author concludes that in LGG, patients with no or only mild deficits at diagnosis, non-awake surgery can no longer be achieved. Indeed, awake craniotomy with intrasurgical electrical mapping has resulted in an increase of the extent of resection and overall survival in LGG. Furthermore, in order to resume a normal familial, social, and professional life, LGG patients with a prolonged survival expectancy have to benefit not only from language mapping when the tumor involves the left "dominant" hemisphere, but also from intraoperative mapping of sensorimotor, visuospatial, higher cognitive, and emotional functions under local anesthesia, even for gliomas situated within presumed "non-language" areas such as the right "non-dominant" hemisphere. In other words, the ultimate goal is to map the functional connectome for each patient in order to perform the resection up to the eloquent networks and then to optimize the onco-functional balance of LGG surgery. To this end, an objective neuropsychological assessment has to be achieved in a more systematic manner before and after resection. Early postoperative cognitive rehabilitation is also recommended, whenever needed.

Keywords Awake surgery · Low-grade glioma · Quality of life · Cognition · Electrical mapping

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Introduction

Supratentorial diffuse low-grade glioma (LGG) is a premalignant brain neoplasm that grows continuously, migrates along the white matter tracts, and inevitably progresses to a higher grade of malignancy, resulting in cognitive as well as neurological deficits, and ultimately to death [15]. This tumor usually occurs in young adults with no or only slight functional disorders, that can be explained by neuroplastic mechanisms that enable a neural network reshaping in reaction to the slow progression of the glioma [11]. Although LGG is the most often diagnosed because of epilepsy, incidental discovery is nowadays more frequent as access to neuroimaging increases worldwide. Such an early detection starts to raise the question of a preventive surgical resection [25]. Maximal LGG removal is significantly increasing the overall survival (OS), as extensively demonstrated in the recent literature based upon the objective measurement of the extent of resection (EOR) on T2/FLAIR-weighted MRI [2, 15, 23, 31, 33, 34]. Indeed, while OS was about 6 years in case of single biopsy [23, 31], the survival is now around 14–15 years when extensive tumor removal has been achieved at diagnosis [2, 23]. As a consequence, precocious radical surgery represents the first therapy in LGG patients [15, 18], provided that the quality of life (QoL) is preserved [10, 17].

In this setting, it is worth noting that neurocognitive and behavioral impairments are more frequent than classical thoughts after LGG surgery, as shown when objective postoperative neuropsychological examinations are performed (for a review, see [24]). In other words, the standard neurological assessment is too crude to be capable to detect subtle deficits; therefore, the negative consequences of surgery on cognitive functions have undoubtedly been underestimated in the traditional literature. To minimize the risk of permanent postoperative deficits, awake surgery has been increasingly used in neuro-oncology in the past two decades, especially in LGG patients who have long survival expectancy. The seminal principle is to combine intrasurgical cognitive monitoring throughout the resection with direct electrostimulation mapping (DEM) of cortical and white matter pathways in order to achieve a real-time investigation of the neural networks. DEM elicits a transitory virtual disruption within a cerebral subcircuit (and not an inactivation of a discrete area, which represents only an entry gate within a larger subnetwork), resulting in specific functional disturbances that will be reproduced when DEM will be repeated over the same structure [16]. Therefore, this technique allows the identification and preservation of both the cortex and the subcortical connectivity crucial for brain processes, based upon online structural-functional correlations done with great precision and reliability [15].

Yet, although the use of DEM led to an increase of the EOR while minimizing the postsurgical persistent morbidity, even in so-called eloquent areas [8], it is puzzling to note that the vast majority of neurosurgeons took the habit in clinical routine to awake LGG patients only for language mapping, most of the time when the tumor involved the left "dominant" hemisphere, whereas the other sensorimotor, visuospatial, cognitive, and emotional functions are generally not tested under local anesthesia if the glioma is situated in presumed "non-language" structures—in particular in the right "non-dominant" hemisphere (for a recent review on this topic, see [38]). Thus, the question is to know whether non-awake craniotomy for supratentorial adult LGG treatment is still feasible if one would like to optimize the onco-functional balance of surgery by maximizing the EOR while preserving or even improving QoL of the patients.

In this short review, the purpose is to summarize the previous literature addressing this issue and to draw a conclusion in the light of our current knowledge.

Material and methods

The PubMed database was searched for all publications using MeSH terms "awake surgery", "low-grade glioma", and "quality of life". References in each included study were checked to find additional relevant studies.

Selection criteria

Searches were restricted to: (1) English-language literature (2) dedicated to LGG in adults (3) who underwent awake surgery (4) and with evaluation of quality of life.

Results

The search process found a total of 31 papers, with 26 of them finally selected according to the above criteria. Indeed, due to the paucity of articles on this topic, all papers but five (two in French, two with no awake mapping, and one dedicated to LGG in children) have been selected. They comprised ten clinical studies, three case reports, and 13 reviews.

The ten clinical studies (including one series on incidental LGG detailed in two complementary articles) have reported 201 cases of LGG who underwent surgical resection under local anesthesia with intraoperative DEM as well as postoperative evaluation of cognition and/or return to work [1, 4, 5, 7, 25, 26, 28, 29, 35–37] (Table 1). Mean age at surgery ranged between 33.5 and 43 years. The presenting symptom was seizure in the vast majority of cases. Although the standard neurological examinations were largely normal (low rate of preoperative deficits, range from 0 to 33%); however, on accurate neuropsychological assessments, cognitive disturbances were frequently observed—ranged between 20 and 91%. Only 20% of tumors were removed in the right hemisphere. The mean EOR volumetrically calculated on postoperative MRI in all series but one was 90% (range 68–100%). Despite a high rate of postoperative neurological worsening in the immediate postoperative period, ranging between 33 to 100%, there were no severe permanent deficits. The late postoperative cognitive status was stable to improve in most of cases, in several series following a postsurgical neuro-rehabilitation. However, disturbances of working memory, attention, executive functions, speed processing, and mood may persist or even may worsen after surgery, hampering the return to work—especially in cases of intractable seizures.

The three case reports showed that it was possible to use fractionated resection in order to remove LGG involving Broca's area without causing persistent deficits thanks to mechanisms of brain plasticity [39], that it could be important to awake singer to map and preserve the pathways underlying the song, especially for LGG involving the right frontal lobe [21], that other subtle functions like smell and taste remain difficult to test and to preserve intraoperatively [30].

The 13 reviews insisted on the need to maximize the EOR in LGG, with the aim of increasing OS while preserving the QoL thanks to awake surgery with intrasurgical mapping by means of DEM both at cortical and subcortical levels [6, 10, 12, 14, 16, 18, 20, 22, 27, 33, 34, 38, 40]. Indeed, due to a

Table 1 Overview of the 10 clinical studies on awake surgery for LGG with evaluation of cognition/return to work

Authors [ref]	Year of publication	No of included patients	Mean age at surgery (years)	Seizure as presenting symptom	Pre-op neurological deficits	Pre-op neurocognitive deficits	Side of the tumor	Mean extent of resection	Early post-op deficits	Late post-op severe neurological deficits (> 3 months)	Late post-op cognitive status (> 3 months)
Teixidor et al. [37]	2007	23	34	91%	4.4%	91%, mainly WM	18LH, 5RH	94%	65.2%	none	Stable to improve in all cases after cognitive rehabilitation
Benzagmout et al. [1]	2007	7	34	100%	none	43%, mainly WM	7LH	85% total or subtotal	100%	none	No deficit after cognitive rehabilitation
De Benedictis et al. [7]	2010	9	39	100%	33%	44%, mainly WM and attention	8LH, 1RH	96.5%	44%	none	Stable to improve in all cases after cognitive rehabilitation
Moritz-Gasser et al. [28]	2012	23	38	100%	none	NA	21LH, 2RH	89.6%	NA	none	No deficit on cognitive scores but increase of reaction time for naming in 47% of cases hampering a return to work
Santini et al. [35]	2012	22 (14LGG)	NA	NA	KPS ≥ 70 in all cases	59%, mainly verbal and visuospatial memory, word fluency and mood	22LH	100% total or subtotal	43% (in LGG)	NA	For LGG: no significant differences with preoperative scores
Schucht et al. [36]	2013	64	33.5	100%	None, mean KPS score 74	NA	45LH, 19RH	92.5%	NA	none	Improved mean KPS score to 80, but 7.8% of functional disorders mainly related to intractable epilepsy preventing a return to work
Chan-Seng et al. [4]	2014	8	41.7	87%	14%	NA	7LH	94.8%	100%	none	Cognitive scores NA but return to work in all cases
Lima et al. [25] and Cochereau et al. [5]	2015/2016	21	35	none (Incidental LGG)	none	60%, mainly executive functions, WM and attention	15LH, 6RH	97%	33%	none	Stable (still ≈60% of poor cognitive functioning) with return to work in all cases
Racine et al. [29]	2015	22	38.4	72.7%	20%	32%, mainly memory	20LH, 2RH	87.4%	55%	none	≈ 50% new concerns in language, fatigue or mood
Mandonnet et al. [26]	2015	24 (10LGG)	43	66%	8.3%	20%, mainly speed processing	20LH, 5RH	68% (for LGG)	16%	none	For LGG: stable to improve in 2/3 of cases; deteriorated in 1/3 of cases; return to work in 87.5% of cases

LGG low-grade gliomas, *NA* not available, *KPS* Karnofsky performance status, *WM* working memory, *LH* left hemisphere, *RH* right hemisphere considerable interindividual anatomo-functional variability, especially in the case of LGG which may induce brain reorganization, it is crucial to detect and preserve neural networks essential for brain functions throughout the resection. In other words, in spite of advances in functional neuroimaging, this technique is not reliable enough to allow maximal safe resection without intrasurgical cognitive monitoring and electrical mapping. In addition, sparing the white matter tracts is critical, because the subcortical connectivity represents the main limitation of neuroplastic potential. Therefore, mapping the cortex is important but not sufficient to avoid postoperative permanent deficits. Finally, because the LGG patients have currently a longer life expectancy about 15 years, more subtle cognitive and behavioral functions should be evaluated in a systematic way (beyond movement and language), since they are crucial to resume a normal familial and socio-professional life. As a consequence, authors have recently proposed to perform awake surgery in all LGG patients with no or only slight preoperative disorders, whatever the tumor location, in order to optimize the quality of cognitive monitoring and mapping during the resection. In other words, even in right LGG, an accurate evaluation of brain functions as dual-task, working memory, attention, judgment, verbal and non-verbal semantics, visuospatial cognition, speed processing, and mentalizing should be achieved to limit the risk of persistent neurocognitive deficits still regularly observed following glioma surgery.

Discussion

To answer the question whether non-awake craniotomy for supratentorial adult LGG treatment is still feasible, this short review of the literature gave several valuable information.

Firstly, regarding oncological considerations, despite the lack of class I evidence, a large amount of data has demonstrated the significant impact of maximal surgical resection on OS in LGG [2, 15, 18, 23, 31, 33, 34]. To optimize the EOR, it has been proposed to perform on an earlier surgery, eventually in incidental LGG, because the tumors are smaller, allowing an increase of the rate of complete or supracomplete resections [25, 40]. However, in essence, this means that the QoL in LGG patients with early diagnosis and management is better before any treatment, and that surgical morbidity has to be imperatively minimized, not only with respect of neurological status but also concerning higher cognitive functions and emotional aspects.

Secondly, awake surgery is currently the gold standard for cerebral mapping [13, 22, 33] because this is the sole technique enabling a direct identification of neural networks crucial for brain functions—whereas functional neuorimaging is able to provide only indirect information [17]. Interestingly, it was evidenced that the use of intraoperative DEM in LGG resulted in an increase of the EOR [7], an improvement of the OS [3], as well as a significant reduction of the rate of postoperative persistent deficits [8]. Indeed, to optimize the onco-functional balance of surgery [10, 17], the concept underlying functional mapping-guided resection is to continue such a resection up to individual critical boundaries, with no margin left around the structures essential for brain functions [14].

Thirdly, DEM in awake patients allows the mapping of both the cortical areas as well as the white matter fibers. Of note, even though functional reshaping is frequently observed in slow-growing LGG, the plastic potential is low at the subcortical level—conversely to the huge potential of cortical neuroplasticity [11, 12]. For example, when a glioma involves the so-called eloquent cortical regions, such as the Broca's area, it is possible to remove it with no permanent deficits, eventually by using multiple-stage surgeries [20, 39]. On the other hand, damaging the subcortical pathways during surgery has a high risk to result in a persistent impairment, because the functional connectivity is the limitation of neural redistribution. In other words, a better understanding of the connectome is crucial at the individual level, that is, the comprehension of the dynamic organization of the whole cortico-subcortical circuitery in real-time throughout the resection [11, 16]—and not to be content with a simple surface mapping before removing the tumor.

Fourthly, an objective assessment of pre- and post-operative neurocognition and QoL is mandatory, because this review shows that subtle neuropsychological disturbances are more frequent than reported in the traditional literature based on simple neurological examinations. Indeed, very few series investigated cognition and emotion in LGG surgery [24]. Nonetheless, in series with objective neuropsychological evaluation, deficits of executive functions, working memory, attention, speed processing, or affect have frequently been observed [26, 28, 29], even in patients with incidental LGG [5]. Importantly, these disturbances, which have been underestimated for a long time, may have negative consequences on the daily life, in particular with regard to the employment outcomes [26, 28]. Interestingly, there is an emerging trend towards following similar practices for the management of LGG in the European Low-Grade Glioma Network, with the proposal of a systematic and similar cognitive assessment protocol [32].

Fifthly, optimizing the onco-functional balance means that the neural foundations of these complex functions, i.e., the functional connectome, should be better studied by the neurosurgeons for each patient [11, 16]. As a consequence, awake surgery has to be more systematically considered in LGG patients with no or mild disorders before any treatment, independently of the localization of the glioma. Indeed, what we have learned from the researches in cognitive neurosciences is that the brain is organized in parallel and interactive,

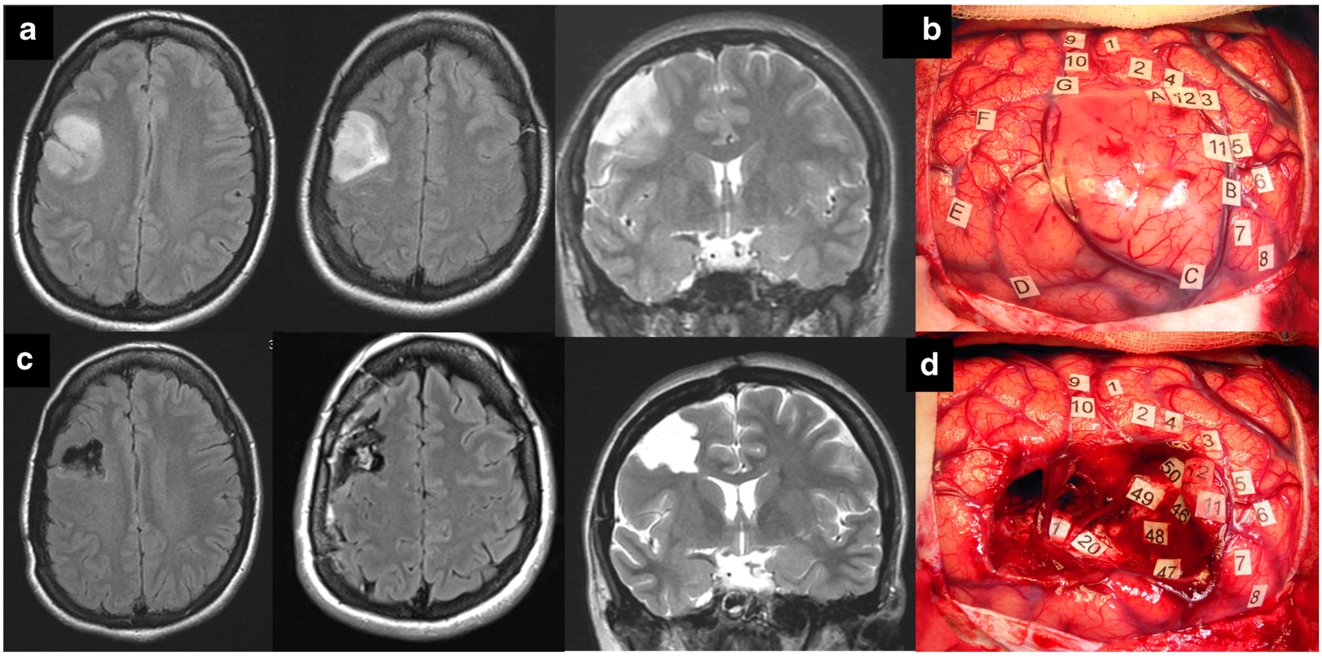

Fig. 1 **a** Preoperative axial FLAIR-weighted and coronal T2-weighted MRI showing a right frontal diffuse low-grade glioma in a 33-year-old right-handed female who experienced seizures. The neurological examination was normal. However, the preoperative neuropsychological evaluation revealed mood disorders, deficit of attention, and working memory, as well as some missing words. **b** Intraoperative view before resection in awake patient. The anterior part of the right hemisphere is on the left and its posterior part is on the right. Letter tags correspond to the projection on the cortical surface of the tumor limits identified using ultrasonography. Number tags show zones of positive direct electrostimulation mapping as follows: 1 and 2: ventral premotor cortex (inducing anarthria during counting task); 3 and 4: negative motor areas (eliciting both speech arrest and interruption of the movement of the left upper limb during dual task); 5 and 6: primary sensorimotor cortex of the upper limb (evoking complex dystonic movements); 7 and 8: primary motor cortex of the hand (generating involuntary movements); 9 and 10: pars opercularis of the inferior frontal gyrus (causing phonological disturbances); 11: mesial part of the dorsolateral prefrontal cortex (inducing semantic disorders during a semantic association task); 12: lateral part of the dorsolateral prefrontal cortex (eliciting disorders of theory of mind during a mentalizing task). **c** Preoperative axial FLAIR-weighted and coronal T2-weighted MRI, demonstrating a complete resection. The patient resumed a normal familial, social, and professional life within 3 months after surgery, with an improvement of the neuropsychological assessment following a postsurgical cognitive rehabilitation. **d** Intraoperative view after resection, achieved up to eloquent structures, both at cortical and subcortical levels. Indeed, direct electrostimulation of white matter tracts enabled the identification of the following functional neural networks; the anterior part of the superior longitudinal fasciculus (lateral portion) running to the ventral premotor cortex, and evoking articulatory disorders (tag 46): this pathway represented the posterior and deep limit of the resection; the frontal part of the inferior fronto-occipital fasciculus, with a branch running to the dorsolateral prefrontal cortex, and causing semantic disorders (tag 50) when stimulated: this pathway represented the postero-lateral limit of the resection; the frontal part of the inferior fronto-occipital fasciculus, with a branch running to the fronto-polar cortex, and generating disorders of theory of mind (tags 1 and 20) during stimulation: this pathway represented the anterior and deep limit of the resection; the oculomotor fibers, generating involuntary left saccades and attention disturbances (tag 49) during stimulation: this pathway represented the postero-lateral and deep limit of the resection; the fronto-striatal tract, inducing arrest of movement of the left upper limb (tag 48) and the left lower limb (tag 47) when stimulated: this pathway represented the postero-mesial and deep limit of the resection

delocalized, large-scale networks frequently distributed on both hemispheres—breaking with the dogma of localizationism [13]. In this connectomal view of cerebral processing, a recent study demonstrated that the right "non-dominant" hemisphere was critical for many brain functions, as control of movement, visuospatial cognition, attention, non-verbal semantics, and theory of mind, even in right-handed patients [38] (for a typical illustration, see Fig. 1). Such data support the need to achieve an accurate monitoring of these higher cognitive and emotional functions in awake patients during LGG resection, whatever the location and the side—challenging the traditional view of awake procedure in the left hemisphere for language mapping versus resecting the tumor under general anesthesia in the right hemisphere [9, 38]. Once again, it is worth noting that objective neuropsychological assessments have usually not been performed after non-awake surgery in most studies in the classical literature, that nonetheless claimed that the patients had no deficits, whereas cognitive disturbances have often been observed in the rare series with postoperative evaluation of high-order functions [24, 26, 28, 29].

Last but not the least, it seems that postoperative neuro-rehabilitation with individualized programs tailored on the basis of the results of pre- and post-operative neuropsychological evaluations, could help the functional recovery, especially with a salutary effect on short-term cognitive complaints as well as on longer-term cognitive performance and mental fatigue, as demonstrated by a randomized controlled trial [19]. Therefore, such a cognitive rehabilitation may facilitate the return to work in these young adult patients. To this end, in the European Low-Grade Glioma Network, more centers recommended early rehabilitation, whenever needed [32].

Conclusion

In summary, based upon the currently available data, the author concludes that in LGG patients with no or only mild complaints at diagnosis, non-awake surgery can no longer be achieved. In fact, in order to resume a normal familial, social, and professional life, LGG patients with a prolonged OS expectancy have to benefit not only from language mapping when the tumor involves the left "dominant" hemisphere, but also from intraoperative DEM mapping of sensorimotor, visuospatial, higher cognitive, and emotional functions under local anesthesia, even for gliomas situated within presumed "non-language" areas such as the right "non-dominant" hemisphere. The ultimate goal is to map the functional connectome for each patient in order to perform the resection up to the eloquent networks and then to optimize the onco-functional balance of LGG surgery. To this end, an objective neuropsychological assessment must be achieved in a more systematic manner before and after resection. Early postoperative cognitive rehabilitation is also recommended, whenever needed.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval Not applicable.

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