

# 5-aminolevulinic acid (5-ALA) fluorescence guided surgery of high-grade gliomas in eloquent areas assisted by functional mapping. Our experience and review of the literature

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## Abstract

**Background** Only few data are available on the specific topic of 5-aminolevulinic acid (5-ALA) guided surgery of high-grade gliomas (HGG) located in eloquent areas. Studies focusing specifically on the post-operative clinical outcome of such patients are yet not available, and it has not been so far explored whether such approach could be more suitable for some particular subgroups of patients.

**Methods** Patients affected by HGG in eloquent areas who underwent surgery assisted by 5-ALA fluorescence and intra-operative monitoring were prospectively recruited in our Department between June 2011 and August 2012. Resection rate was reported as complete resection of

enhancing tumor (CRET), gross total resection (GTR) >98 % and GTR>90 %. Clinical outcome was evaluated at 7, 30, and 90 days after surgery.

**Results** Thirty-one patients were enrolled. Resection was complete (CRET) in 74 % of patients. Tumor removal was stopped to avoid neurological impairment in 26 % of cases. GTR>98 % and GTR>90 % was achieved in 93 % and 100 % of cases, respectively. First surgery and awake surgery had a CRET rate of 80 % and 83 %, respectively. Even though at the first-week assessment 64 % of patients presented neurological impairment, there was a 3 % rate of severe morbidity at the 90th day assessment. Newly diagnosed patients had a significantly lower morbidity (0 %) and post-operative higher median KPS. Both pre-operative neurological condition and improvement after corticosteroids resulted significantly predictive of post-operative functional outcome.

**Conclusions** 5-ALA surgery assisted by functional mapping makes high HGG resection in eloquent areas feasible, through a reasonable rate of late morbidity. This emerges even more remarkably for selected patients.

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**Keywords** Cortical and sub-cortical stimulation · Functional mapping · High grade glioma · Eloquent areas · Fluorescence-guided tumor resection · Intra-operative monitoring · Neuronavigation

## Introduction

The current surgical treatment of high-grade gliomas (HGG) is based on maximal safe resection. The degree of surgical

removal has been shown to play an important role in the overall survival of patients [1, 2]. However, the scarce macroscopic distinction between healthy and pathological tissue in HGG infiltration zones makes maximal resection challenging to achieve. A recent study concerning surgical outcome on a large GBM case series reported a gross total resection (GTR) rate between 21 and 49 % [3]. 5-ALA oral administration before surgery allows the intra-operative detection under blue-violet light of tumor tissue that would not be visible otherwise under white light [4]. Fluorescence intensity (bright and “vague”) is associated with solid tumor and invasive areas with 100 % and 97 % positive predictive value, respectively [5]. Data are available from a recent randomized controlled trial which reported a significant benefit in the extent of HGG resection from fluorescence-guided surgery [6, 7]. Furthermore, data from the same series supported level 2b evidence on the influence on survival of total resection [7]. GTR ought to be the goal for all patients, if performed with a low risk of permanent neurological deficit. In spite of this, the very limited life expectancy of these patients entails that preserving function to maintain or even improve quality of life becomes an issue of primary importance for clinicians. There is also some evidence that the development of new postoperative motor or language deficits seems to be associated with decreased overall survival, despite similar extents of resection and adjuvant therapy [8]. Functional mapping plays a pivotal role in modern neurosurgery; nonetheless, the clinical outcome after maximal resection pursued in eloquent areas when intra-operative monitoring and 5-ALA fluorescence are used together remains unclear. Few data have been published on this issue so far, and whether this approach might be more suitable for some subgroups of patients has not been explored. Furthermore, studies focusing on the post-operative clinical outcome of such patients are yet not available.

## Methods

### Patient population

We screened for surgery with 5-ALA all patients consulting our unit whose MRI scans were suggestive of HGG, from June 2011 until August 2012. Resectability was decided on the basis of T1-weighted gadolinium magnetic resonance imaging (T1-GdMRI). Inclusion criteria for enrolment were: MRI suggestive for HGG, complete surgical removal deemed possible at pre-operative assessment, tumor location close to eloquent areas, plan for surgery guided by 5-ALA fluorescence with the assistance of MRI neuro-navigation (TIGd) and intra-operative monitoring, both in asleep and awake condition. Tumor location was analyzed on contrast-

enhanced T1 sequences and the proximity to eloquent structures was assessed with diffusion tensor and functional magnetic resonance imaging (MRI) images. Following previous authors [1, 9, 10], the following areas were regarded as eloquent: primary motor and sensory cortex, the basal ganglia, thalamus, hypothalamus, cerebral peduncles, the brainstem, the dentate nucleus, the presumed language areas (identified by fMRI), the primary visual cortex, and essential white matter tracts linked to these eloquent regions (identified by DTI). Only tumors close (less than 10 mm) to eloquent structures were enrolled. Tumor location and distance by eloquent areas were defined by an expert neuroradiologist based on preoperative magnetic resonance imaging (MRI). Informed consent was obtained from all patients. Tumor grade was histologically confirmed in all cases.

### Tumor resection and intra-operative monitoring

Patients were administered 20 mg/kg 5-aminolevulinic acid orally 2–4 h before surgery, as previously described [3]. All operations were performed with a Zeiss Pentero microscope equipped with a fluorescent 400-nm UV light and filters. All patients were operated on in a MRI-neuronavigational setting. Diffusion tensor and functional magnetic resonance imaging (MRI) were performed to visualize functional cortical areas and cerebral fiber tracts, and subsequently loaded in the neuronavigational system. Microsurgical removal was started using a standard white xenon light and switched to the violet-blue excitation light whenever tumor boundaries were visually indistinct from healthy brain tissue. At the end of resection, the cavity was systematically checked in the violet-blue light mode for any residual tumor. In the cases in which resection was stopped and residual fluorescent tissue was still present in the boundaries, the fluorescence intensity was recorded (as bright or vague fluorescence) [3].

With regard to the functional area involved, intra-operative monitoring was performed on either in asleep or in awake surgery, depending on both patient and tumor features.

A standard intra-operative surgical and neurophysiological protocol was followed for all patients. Such protocol entailed MRI neuronavigation and continuous electroencephalography (EEG), electrocorticography (ECoG), and multi-channel electromyography recordings. Monitoring included tracking of motor-evoked potentials (MEPs), sensory-evoked potentials (SEPs), and cortical and subcortical stimulation. Cortical and subcortical stimulations were performed in order to localize functional areas and cortical tracts surrounding the lesions. The multi-pulse stimulation technique was adopted. Such stimuli were applied using a monopolar probe in asleep patients and a bipolar probe in awake patients. A functional cortical map was obtained

using the electrostimulation method described by other authors [11]. The intensity of the electric current ranged from 1.5 to 8 mA. Tumor was removed by alternating resection and subcortical stimulations. Criteria to stop resection were two: first, the lack of tumoral tissue at white light and of fluorescent tissue at final blue light control. Second, the localization of either a functional area or a cortical tract during fluorescent tissue resection.

#### Research variables

Our study focused on defining both the extent of resection and the clinical outcome of patients affected by HGG in eloquent areas who underwent surgery assisted by 5-ALA fluorescence and intra-operative monitoring. The main purpose of the study was the analysis of the post-operative clinical outcome of such patients. Neurological assessment was performed pre-operatively, and then at the 7th day, at 1 month, and at 3 months after surgery. Clinical assessment was performed only by one neurosurgeon and one speech therapist, in order to avoid inter-observer variability. The degree of motor impairment was scored using a standardized motor scale [12] as follows: 0, no deficit; 1, mild deficit (patient can use the affected limb almost normally); 2, moderate deficit (movement is possible with help from the examiner); and 3, severe deficit (no spontaneous movement against gravity). The degree of speech impairment was scored as follows: severe, middle, mild, minimal [13]. Patients with severe aphasia show great difficulty in understanding and producing spoken and written language. Middle aphasia is characterized by the ability to talk about familiar topics with the help of an interlocutor. In mild aphasia the patient is able to talk about most everyday topics with minimal help. Patients with minimal aphasia show reduction in speech fluency with mild signs of aphasia. Finally, we evaluated the Karnofsky performance status (KPS) score for each patient [14]. MRI studies were performed with a 1.5-T GE scanner. According to previous authors [1, 15, 16] extent of resection was reported as complete (complete resection of enhancing tumor [CRET]), more than 98 % and more than 90 %. Sub-total resection was a residual volume less than 90 %. All MRI studies included fluid-attenuated inversion recovery, T2-weighted and T1-weighted, before and after administration of gadolinium (Gd)-contrast medium (gadopentetate dimeglumine). A volumetric Gd T1-weighted MRI study was finally performed. Control MRI was performed within 72 h from surgery, in order to evaluate degree of removal. The extent of resection of enhancing tissue was carefully measured by an expert neuroradiologist, comparing volumetric postoperative magnetic resonance imaging (MRI) with volumetric preoperative MRI. Our study finally stratified the data for specific subgroups of patients, in order to assess if the

reported multimodal approach was more suitable for selected cases. With this purpose, recurrent surgery, surgical technique (Asleep versus awake surgery), tumor grade (IV versus III WHO grade) were analyzed. Age, tumor size, corticosteroid treatment, pre-operative neurological deficit and its improvement after corticosteroid use were also recorded.

#### Statistical analysis

Analysis between first surgery, morbidity rate, KPS, corticosteroid treatment and post operative neurological assessment was performed via  $\chi^2$  test in two-way tables. If any value was <10 in the two-way table, Fisher's exact test was used.

#### Results

Thirty-one patients (20 males and 11 females) were enrolled (Table 1). The median age was 57 years (range 27–79 years). Twenty-two patients were affected by newly diagnosed gliomas, while nine patients had second surgery for recurrent glioma. Twenty-seven of them presented a KPS of 100. The mean tumor volume before surgery was 28.2 cm<sup>3</sup> (range 0.9–71 cm<sup>3</sup>).

Histopathological results showed that patients harbored glioblastoma (WHO Grade IV) in 25 cases, anaplastic astrocytoma (WHO Grade III) in 4 cases, anaplastic oligodendroglioma (WHO Grade III) in 2 cases. 25 patients were operated on in asleep surgery, and 6 patients in awake surgery. All patients underwent corticosteroid treatment, with 12 mg of desametasone/day for at least 5 days.

**Table 1** Clinical and surgical characteristics of patients

Parameter	No.
No. of patients	31
Newly diagnosed	22
Recurrent	9
Tumor grade	
Grade IV glioma	25
Grade III glioma	6
Tumor location	
Sensimotor area	19
Right insular region	6
Left fronto-temporal (language areas)	6
Monitoring	
Asleep	25
Awake	6
Median pre-operative KPS score	100

Preoperative impairment was detected in 9 cases: 3 of these completely recovered within a few days after preoperative corticosteroid treatment was started. All patients started a radiotherapy protocol with concomitant temozolomide-based chemotherapy within 6 weeks after surgery.

Extent of resection and fluorescence data

In all 31 cases the tumor presented areas of bright fluorescence. Extent of resection data are summarized in Table 2. Patients were divided into three groups according to extent of resection and functional mapping data. CRET (complete resection of enhancing tumor) was achieved in 23 patients. In 8 out of 31 patients (Fig. 1) the resection was stopped because a functional area or cortical tract was identified or because MEP amplitudes were reduced in an area where fluorescent tumor cells were still visible (Fig. 2). In all these 8 patients, bright fluorescent tissue was detected at final control. Residual tumor less than 2 % at post-operative MRI was detected in 6 patients. In 2 out of 31 patients resection between 90 % and 98 % was achieved. We analysed the connection between the extent of resection and both tumor grade and repeated surgery. In Grade III glioma patients, complete, >98 and >90 % resection was achieved in 3, 2 and 1 cases; conversely, in grade IV gliomas complete, >98 and >90 % resection was achieved in 20, 4, and 1 cases. Resection was complete and more than 98 % in 18 and 4 newly diagnosed patients. In recurrent cases, resection was complete in 5, >98 % in 2 and >90 % in 2 cases. Lastly, GTR was achieved in 5 out of 6 patients operated on in awake surgery.

Functional outcome

Preoperatively, 6 patients presented neurological impairment: it consisted of hemiparesis in 5 cases (grade 1 in four cases and grade 2 in one case), and minimal aphasia in 1 case. Three additional cases completely recovered before surgery with corticosteroid treatment (motor impairment in 2 cases, language deficit in one case). Data concerning neurological outcome are summarized in Fig. 1. At the 7th-day assessment, 20 patients presented neurological impairment. The postoperative neurological status worsened in 19 cases: indeed, 5 out of 19 patients had a further impairment of a previous deficit and 14 out of 19 presented a new

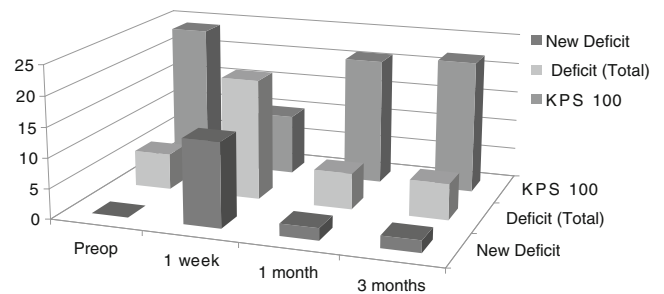


Fig. 1 Preoperative and postoperative conditions of patients. KPS 100: Patients with KPS of 100. Deficit (Total): Patients affected by neurological deficit. New deficit: Patients affected by a new neurological deficit. Data are expressed in number of patients (see text for details)

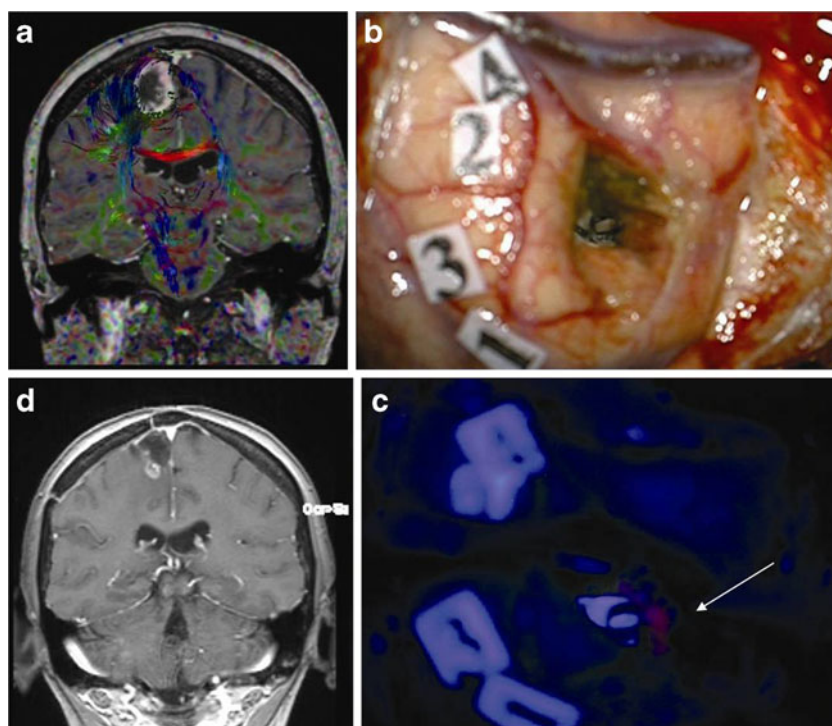
deficit, whilst it was unchanged in 1 case. At the first month evaluation, 14 out of 20 patients fully recovered, while 6 patients presented neurological impairment: among these, 4 were unchanged in comparison with pre-surgical condition, and 2 maintained their postoperative new deficit unchanged (one patient with a grade 2 and one patient with a grade 3 motor impairment). A median KPS score of 100 was detected in 27 patients before surgery, in 13 at 1 week, in 24 at 1 month, and in 25 at 3 months after surgery. We considered the potential connection between neurological outcome and repeated surgery. At first-week assessment, a new neurological deficit affected 6 out of 9 and 14 out of 22 patients with recurrent and newly diagnosed disease, respectively, whereas at first-month assessment new deficits were detected in 2/9 patients who had surgery for recurrent disease, and in no patients with a new diagnosis (0/22). KPS was 100 in 1 out of 9 and in 12 out of 22 at 1 week, and 4 out of 9 and 21 out of 22 at 3 months after surgery of recurrent and newly diagnosed glioma patients, respectively. Finally, we analysed the connection between neurological outcome and grade of tumor. At first-month assessment, new deficit affected 3 out of 6 and 17 out of 25 at 1 week, and 0 out of 9 and 2 out of 22 of patients at 1 month with grade III and grade IV glioma, respectively. At the 3-month postoperative assessment, KPS was 100 in 5 out of 6 and in 8 out of 25 at 1 week, and 5 out of 6 and 20 out of 25 of grade III and grade IV glioma patients respectively. We also considered the potential connection between preoperative status and post-operative course. Among patients with preoperative deficit, 5 out of 6 and 4 out of 6 presented a postoperative worsening at 1-week and 1-month assessment,

Table 2 Data on extent of resection

	Resection rate	Total cases n (%)	Gr. IV cases n (%)	Gr. III cases n (%)	ND cases n (%)	Rec cases n (%)
CRET complete resection of enhancing tumor; Gr IV Glioma grade IV (sec. WHO); Gr III glioma grade III (sec. WHO); ND newly diagnosed; Rec recurrent	CRET	23 (74 %)	20 (80 %)	3 (50 %)	18 (81 %)	5 (56 %)
	>98 % <100 %	6 (19 %)	4 (16 %)	2 (34 %)	4 (19 %)	2 (22 %)
	>90 % <98 %	2 (6 %)	1 (4 %)	1 (16 %)	0 0	2 (22 %)



**Fig. 2** Gross total resection (>90 %<98 %) of a newly diagnosed right motor area grade IV glioma operated on in asleep surgery. **a** Preoperative coronal T1Gd and DTI MRI shows glioma and connection with motor pathway. **b** Intra-operative final images under white light. One to four flags correspond to motor area. 6 flag corresponds to subcortical identification of cortico-spinal tract that steered resection. **c** Intra-operative final images under blue light. Fluorescence is still evident (*white arrow*) in close proximity to cortico-spinal tract (tag 6). **d** Post-operative coronal T1Gd image shows extent of resection



respectively. Among patients without preoperative deficits, 14 out of 25 and 2 out of 25 presented a post-operative new deficit at 1-week and 1-month assessment, respectively.

Among 25 patients without pre-operative deficits, all 3 patients with neurological deficit who had pre-operatively recovered after corticosteroid administration presented a new deficit at 1st week assessment, and one case recovered at 1st month and 3rd month evaluation. Among 22 patients who never experienced a neurological deficit in the preoperative stage, a new deficit was detected in 11 at 1st week, while no new deficits were detected at 1 and 3 months after surgery. Post-operative course was similar despite age (<65 vs. >65 age patients) and tumor size. The 5-ALA administration was well tolerated with no adverse effects, and showed fluorescent tumor tissue in all cases. In one case an intra-operative seizure because of repeated cortical stimulation was recorded.

## Discussion

Our present relevant results

Complete resection (CRET) was achieved in 74 % of cases. In 93 % and in 100 % of patients, the extent of resection was more than 98 % and more than 90 %, respectively. In 26 % of cases, tumor removal was intentionally stopped to avoid neurological damage.

We did not detect any significant association between histopathological grade and extent of resection: GTR was

achieved in 50 % of grade III and in 76 % of grade IV glioma. No connection was observed between extent of resection and recurrent surgery. Our data document that GTR was accomplished in 76 % of newly diagnosed and in 66 % of recurrent tumors. Even if not statistically significant, GTR rate was particularly high among patients operated in awake surgery (83 %).

Functional data were analyzed. Only 3 % of patients presented a severe postoperative new deficit. As a matter of fact, 70 % of patients who suffered an immediate post-surgical impairment presented a full recovery. In the small subgroup of patients who had their surgery in awake condition, late morbidity was 0 %. A significant association was observed between neurological outcome and surgery for recurrent disease: 100 % of patients with permanent post-operative impairment were affected by a recurrent tumor. First surgery was significantly associated with a lower morbidity (P value<0.05) and to an higher KPS (P value<0.01). Conversely, we did not find any connection between neurological outcome and tumor grade.

Pre-operative clinical status was predictive of post-operative outcome: 1-month morbidity, meant as the post-operative worsening of a pre-operative deficit or as a new post-operative deficit, was significantly associated to the presence of a pre-operative neurological deficit and corticosteroid responsiveness. In particular, patients with preoperative impairment presented a morbidity rate of 67 %, as opposed to the 8 % morbidity rate of patients who were not preoperatively impaired (p=0.006). Patients with a neurological deficit which was subject to improvement after

corticosteroid treatment before surgery had a worse outcome compared to those who approached surgery with no neurological symptoms (morbidity of 67 % and 0 %, respectively,  $p=0.01$ ). Lastly, only 3 % of patients experienced an intra-operative complication (seizure) due to functional mapping. Despite functional deficits suffered in the post-operative course, in all cases the radio-chemotherapy started within 6 weeks after surgery.

Comparison of our relevant results to those of other studies

We compared our data to those of similar studies published in literature (see Table 3). To the best of our knowledge, there are only three mono-institutional studies reporting data concerning HGG surgery in eloquent areas combining 5-ALA and IOM [10, 17, 18]. However, only Feigl et al. [18] focused their attention on the multimodal approach in eloquent areas. They reported GTR (>98 %) in 64 % in a series of 18 patients. In 24 % of cases, resection was stopped because a functional area or a cortical tract was identified. The reported morbidity was 12 %. The other two studies focused on 5-ALA surgery on gliomas in general, and data about the specific issue of eloquent location need to be extrapolated. Schucht and colleagues [10] reported a CRET of 74 % on 19 patients with tumors in eloquent location who underwent 5-ALA guided resection. Diez et al. did not report resection rate data in this subgroup of patients.

Data on the post-operative course of patients operated with 5-ALA fluorescence and functional mapping were not analyzed in detail. Data on repeated surgery, tumor grade, awake surgery, and pre-operative condition are lacking.

Lastly, we compared our data to those reported in literature concerning the relation between resection and functional outcome in glioma surgery. A 75 % GTR rate with 3 % morbidity was reported with intra-operative monitoring, while a 58 % GTR rate with 8 % morbidity was reported without functional mapping [6, 9, 19–21]. However, resection and morbidity data widely varied, depending on tumor grade, surgical technique, country, different degrees of eloquent area involvement, and different meanings of gross

total removal above all (i.e., >90 %, >95 %, no residual enhancement, etc).

Finally, it must be emphasized that no data have been reported in literature about 5-ALA fluorescence in awake surgery.

Significance of our findings and indications for future research

The design of our study does not allow us to change the current management of high-grade gliomas in eloquent areas. We do appreciate that, in our series, favourable median age and KPS, and exclusive enrolment of radical surgery candidates leads to a pre-selection of patients (selection bias). In addition, proximity to ventricles, extent of oedema, degree of contrast enhancement, are variables that could influence the surgical result.

However, our data provide helpful information on outcome, when an advanced multimodal strategy is applied to this challenging field of neuro-oncological surgery. In our experience, combination of 5-ALA fluorescence, functional mapping, and neuro-navigation has been feasible and reliable. Despite the small number of patients in the presented series, we want to emphasize three main points and report some considerations.

First, maximal resection guided by 5-ALA fluorescence of high-grade gliomas in eloquent areas is achievable in a high percentage of cases through a reasonably low morbidity. The high early post-operative morbidity could be the transient cost of such an aggressive resection. However, we want to emphasize that transient deficit never delayed adjuvant treatments in our series.

Second, the reported multimodal approach for tumors in eloquent areas seems to be more suitable for some patients. Preoperative neurological status and second surgery were strictly predictive of post-operative outcome.

Third, in our experience, blue-violet light was feasible and reliable also in awake surgery. Patients operated in awake condition presented a permanent morbidity of 0. This result is another potential target for future studies with larger

**Table 3** Data from literature

Authors	Total cases				Cases in eloquent areas			
	n. patients	Resection rate CRET GTR>98 %		Morbidity	n. patients	Resection rate CRET GTR>98 %		Morbidity
Feigl et al (J Neurosurg, 2010)	18 <sup>a</sup>	–	64 %	12 %	18 <sup>a</sup>	–	64 %	12 %
Diez Valle et al. (J Neurooncol, 2011)	36	83.3 %	100 %	8.2 %	11	–	–	–
(Schucht et al. Neurosurgery, 2012)	53	89 %	96 %	7.5 %	15	74 %	–	–

CRET complete resection of enhancing tumor. GTR gross total removal

<sup>a</sup> 25 surgical procedure were performed on 18 patients (see text for details)

series. In fact, surgical data obtained from the combination of awake surgery and 5-ALA surgery could be even more surprising.

More generally, our report shows that current surgery of malignant gliomas is not limited by the assessment of tumour boundaries, but rather by functional information that can be obtained by appropriate functional mapping. In this sense, some modern tools such as 5-ALA fluorescence and intra-operative MRI [4] have been proven to be effective in maximizing tumour resection. In our experience, STR was always related to the intentional stopping of resection driven by intra-operative monitoring. This means that the exclusive use of 5-ALA fluorescence alone may not be safe, in terms of postoperative morbidity, whilst the combination between the two techniques is synergistic.

## Conclusions

Even if the interpretation of our results may be biased by enrollment criteria, we think that our study provides meaningful data on patients outcome when an advanced multimodal strategy is applied to this challenging field of neuro-oncological surgery. The benefit of this approach has been shown even more remarkable for selected patients. However, further studies on larger series, mainly focusing on postoperative survival, are needed to prove the actual advantages of this multimodal strategy.

**Conflict of interest** None.

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## Comment

Della Puppa and co-workers combine two modern techniques for malignant glioma surgery, intra-operative mapping/monitoring, and fluorescence-guidance with ALA (Gliolan®). They demonstrate that given modern methods for identifying tumor intra-operatively, function limits resection. Combining both techniques will result in a high rate of complete resections of contrast-enhancing tumors even in a population of patients with gliomas in critical brain areas, with acceptable temporary morbidity. Surgery with methods for resection optimization (ALA, intra-op MRI or a combination) as well as methods for maintaining function should be considered standard for these patients, where there is often a small margin between benefits and pitfalls from what neurosurgeons are doing and safe maximal resection is the goal.

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