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Original Article

Fluorescein for resection of high-grade gliomas: A safety study control in a single center and review of the literature

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Abstract

Background: The importance of a complete resection of high-grade gliomas (HGGs) has been highlighted in scientific literature, in order to limit tumor recurrence and above all to improve disease-free survival rates. Several fluorescent biomarkers have been tested to improve intraoperative identification of residual tumor; 5-aminolevulinic acid (5-ALA) and fluorescein sodium (FS) are now starting to play a central role in glioma surgery. We performed a retrospective analysis on 47 patients operated for HGGs. Here we report our preliminary data.

Methods: Data of 47 consecutive patients with HGG have been collected in our study (25 males, 22 females; mean age: 60.3 years, range: 27–86 years). Fluorescein (5 mg/kg of body weight) was injected intravenously right after the induction of general anesthesia. A YELLOW 560 filter was used on an OPMI Pentero 900 microscope (Carl Zeiss Meditec, Oberkochen, Germany) to complete a microsurgical tumor removal. Glioma resection and quality of life were evaluated preoperative and postoperatively.

Results: Gross total resection (GTR) was achieved in 53.2% (n = 25) of patients. A subtotal resection (STR) (>95%) was achieved in 29.8% (n = 14), while a partial resection (PR) (<95%) was obtained in 17% (n = 8) of patients. Overall, in 83% (n = 39) of patients who underwent fluorescence-guided surgery the resection rate achieved was >95%. No adverse effects correlated to fluorescein have been recorded.

Conclusion: Fluorescein seems to be safe and effective in the resection of HGGs, allowing a high rate of gross total removal of contrast enhanced areas.

Key Words: 5-aminolevulinic acid, extent of resection, fluorescein sodium, high-grade gliomas, YELLOW 560 filter

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INTRODUCTION

Gliomas are the most common primary malignant brain tumors in adults, nearly represent 80%, with poor prognosis in their high-grade forms.[24] According to the current WHO grading system, high grades include grade III and IV lesions. One-year survival rate for high-grade gliomas (HGGs) is 53.7%, while 2-year survival rate for these patients is only 14.6%.[8] Annually, 8,000 new cases are diagnosed in the United States.[18,20] Several variables positively affect the prognosis for patients diagnosed with HGG: these include young age, tumor location, radiological features, recurrence, and the opportunity to perform an adjuvant therapy in the postoperative course.[34] Recent studies identified a strong correlation between removal extent of glioblastomas and overall survival with maximal survival benefit when resection volume is greater than 98% and surgery is followed by adjuvant radiotherapy and chemotherapy.[9,19,29,36] Unfortunately, the similarity between tumor appearance and surrounding brain parenchyma under the operating microscope makes a complete tumor resection challenging.[20] In recent years, fluorescence-guided technology has started to emerge in glioma resection procedures to help the surgeon differentiating intraoperatively neoplastic tissue from normal brain in order to maximize the extent of glioma resection. Several fluorescent biomarkers have been investigated to improve intraoperative identification of residual tumor: 5-aminolevulinic acid (5-ALA) and fluorescein sodium (FS) are the most promising in glioma surgery.[38] 5-ALA, metabolized by some tumoral cell enzymes into the strongly fluorescent protoporphyrin IX, has been used as a metabolic marker in glioma surgery with good results.[9,11] Although its 100% specificity and a 85% sensitivity for tumoral tissues,[27] several elements have limited the widespread of 5-ALA fluorescence to guide gliomas resection: first of all its high costs (more than 900 euros for each vial), but also the way of administration (oral, some hours before the induction of anesthesia) and the high risk of skin sensitization within 24 h after the operation (the patient should not be exposed to sunlight or strong artificial light).[3] On the contrary, FS is a fluorescent substance that can be used for immediate improved visualization of brain tumor tissue, with nonspecificity for tumor cells.[27] This dye, if excited by a light whose wavelength is in the range of 460–500 nm, emits fluorescent radiation with wavelength range of 540–690 nm. FS does not selectively accumulate in astrocytoma cells, but in extracellular tumor sites, suggesting its role as a marker for compromised blood-brain barrier (BBB) areas, as in high-grade astrocytomas. Widely used in ophthalmic surgery, fluorescein is injected intravenously just before glioma resection, it is virtually free of side effects and has low costs, approximately 5 euros each vial (1 g of substance).[3,30] It is usually visible to the naked eye at high dosage (20 mg/kg body weight) and at lower doses, it is observable under the YELLOW 560 nm surgical microscope filter, allowing a better tissue discrimination with more natural colors [Table 1].[10,32] In this study, we report our preliminary data retrospectively collected on 47 patients operated for HGGs. Our aim is to demonstrate the effectiveness and safety of fluorescence-guided surgery in HGG surgery. We focus on histology, tumor removal rate, clinical pre- and postoperative parameters, quality of life, and any adverse effects.[27]

MATERIALS AND METHODS

In this retrospective study, after the approval of Local Ethic Committee, we collected data of 47 patients (25 males, 22 females; mean age: 60.3 years, range: 27–86 years). All patients had been surgically treated at the Neurosurgical Unit of ARNAS Civico Hospital, between September 2015 and November 2016 [Table 2]. Each patient was informed on benefits and risks connected with the study and all of them signed an informed consent. The inclusion criteria were as follows: 1) age between 18 years and 90 years; 2) suspect of HGG (astrocytoma III or IV grade according WHO classification) on the basis of contrast enhanced magnetic resonance imaging (MRI) findings; 3) tumor location that allowed a complete surgical resection of the enhanced area (i.e., no eloquent areas). Exclusion criteria were as follows: 1) severe heart, liver or kidney disease; 2) recent acute ischemic stroke; 3) prior history of adverse reaction to FS or severe reactions to other contrast agents; 4) women during the first trimester of pregnancy; 5) specific neural tumor locations such as corpus callosum, basal ganglia, brain stem, posterior cranial fossa; 6) preoperative KPS (Karnofsky Performance Status) score of 60 or less; 7) tumor diameter <1 cm or >5 cm; 8) history of non-neural malignant tumors.

Surgical protocol

In all cases 5 mg/kg body weight of FS was injected intravenously via the central venous line, after the induction of anesthesia. Vital signs were monitored for 15 min. Under white light, no fluorescent effect was detected. The fluorescent dye was visible under the

Table 1: Brief comparison between 5-aminolevulinic acid (5-ALA) and fluorescein sodium (FS) with their main characteristics

Characteristic	5-ALA	FS
Titer	Peak	Steady-state
Handling	Less	More
Working area brightness	Dark	Optimal
Cost	Elevated	Moderate
Safety	Skin sensitization	Virtually free of side effects

5-ALA: 5-aminolevulinic acid, FS: Fluorescein sodium

YELLOW 560 nm filter, on the OPMI Pentero 900 surgical microscope (Carl Zeiss Meditec, Oberkochen, Germany). The fluorescence shaped the vital tumor margins [Figure 1]. All the procedures were carried out by the same senior neurosurgeon (N.F.); this allowed distinction between cases in which fluorescence was judged "helpful" and cases in which was considered "not helpful", on the basis of a clear intraoperative distinction between the normal brain and the tumor tissue. Neuronavigation was used for tumor localization, mostly for the localization of close eloquent areas. Autologous fibrin glue was used as sealant when necessary.[12,13,22,23] Postoperatively, all the patients were admitted in the neurosurgical intensive care unit (ICU) for postoperative care.

Table 2: Demographic data and presenting characteristic of the patients

Characteristic	Number of patients (%)
Total number of patients	47 (100)
Mean age in years (range)	60.3 (27-86)
Sex	
Male	25 (53.1)
Female	22 (46.8)
Tumor location	
Frontal	13 (27.7)
Temporal	7 (14.9)
Fronto-temporal	8 (17.1)
Fronto-temporo-insular	2 (4.2)
Parietal	9 (19.2)
Fronto-parietal	1 (2.1)
Temporo-parietal	1 (2.1)
Occipital	3 (6.4)
Temporo-parieto-occipital	1 (2.1)
Parieto-occipital	2 (4.2)
Grading	
III	14 (29.8)
IV	33 (70.2)
Preoperative KPS	
70	5 (10.6)
80	19 (40.4)
90	17 (36.2)
100	6 (12.8)

KPS: Karnofsky Performance Status

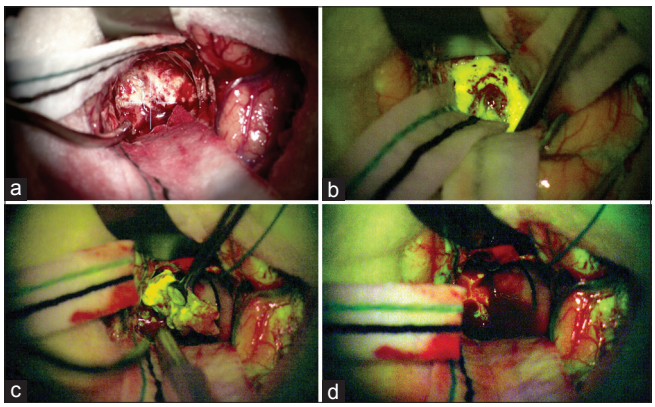

Figure 1: Intraoperative view of a right frontal glioblastoma under normal white xenon-light illumination (a) and at the beginning of tumor removal under the YELLOW 560 nm filter (b). During tumor removal on the Pentero 900 surgical microscope, there is a clear delineation of the tumor area which shows significant fluorescein sodium enhancement revealing the boundary between the bright yellow tumor and the surrounding brain (c); at the end of the removal, no residual tumor tissue is evident (d)

Pre- and postoperative clinical assessment

Each patient general physical performance was recorded using the KPS. The median preoperative KPS score was 85.1 (range: 70–100). Preoperative clinical evaluation was performed at the admission to the neurosurgical unit. A second evaluation was conducted during the postoperative course, on discharge and at the first outpatient clinic visit approximately 1 month later. The neurological exam was evaluated by a neurologist. Surgery was followed by radiotherapy with concomitant and adjuvant temozolomide in 85.1% of cases, according to the Stupp protocol.[37]

Radiological assessment

Postoperatively, the extent of tumor resection was identified by 35 contrast enhanced T1 weighted MRI and 12 contrast enhanced computed tomography (CT scan), 72 h after surgery. Three categories were distinguished: no residual tumor tissue = gross total resection (GTR); minimal residual tumor tissue = subtotal resection (STR) and partial resection (PR). GTR was defined as resection where no residual enhanced tumor is visible, STR was defined as nearly total (>95%), PR as <95%. Postoperative tumor volumes after surgery were calculated using an open-source, free medical image viewer software (*OsiriX for Mac*) on enhanced residual tissue (in T1 weighted MRI or CT scan) [Figures 2 and 3].

Histological examination

Histological analyses were performed with standard procedures. The classification was conducted on the basis of the current WHO classification of tumors of the central nervous system.

RESULTS

The average duration of the surgical procedure ("skin to skin") was 175.5 min (range: 108–316 min); the median length of hospital stay was 20 days (range: 8–73 days). Patients and tumor data and results are summarized in Tables 2 and 3. At neuropathological analysis, 14 patients were diagnosed with anaplastic astrocytoma grade III, while 33 patients were diagnosed with a grade IV glioblastoma, according to the WHO classification. No adverse effects associated with the administration of FS were observed. Yellow staining of sclera, skin, and

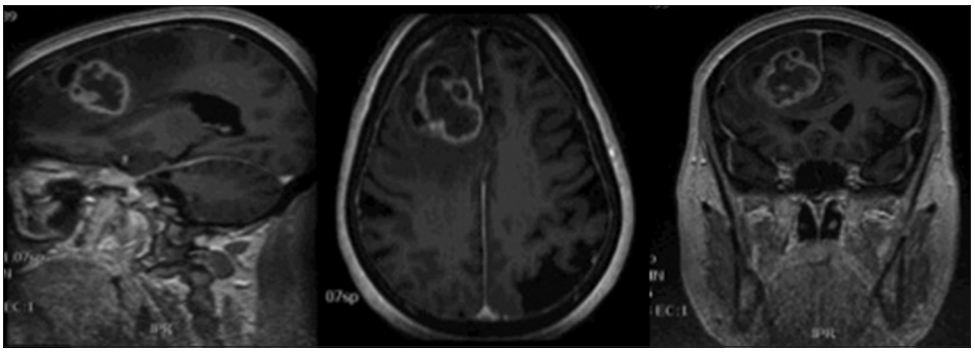

Figure 2: Preoperative neuroimaging of a right frontal glioblastoma. Gadolinium enhanced T1 weighted brain magnetic resonance imaging (MRI)

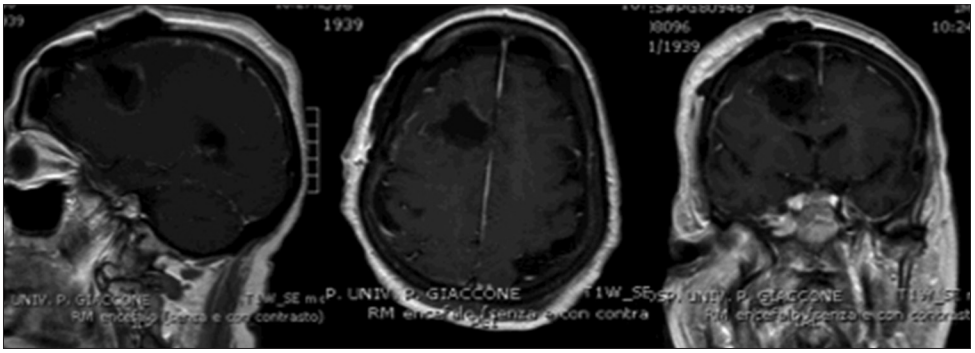

Figure 3: Postoperative neuroimaging of a right frontal glioblastoma. Gadolinium enhanced T1 weighted brain magnetic resonance imaging (MRI)

Table 3: Summary of the results of this observational study

Characteristic	Number of patients (%)
Mean surgical procedure duration (min)	175.5 (range: 108-316)
Mean time of hospitalization (days)	20 (range: 8-73 days)
Tumor removal rate	
GTR	25 (53.2%)
STR	14 (29.8%)
PR	8 (17%)
Complications	
Transient hemiparesis	9
Hemorrhage with permanent hemiparesis	6
Seizures	4
Hydrocephalus	1
Sepsis	1
Postoperative KPS	
Improved	15 (31.9%)
Unchanged	21 (44.7%)
Worsened	11 (23.4%)

GTR: Gross total resection, STR: Subtotal resection, PR: Partial resection

urine disappeared within approximately 24 h after the surgical procedure. No abnormal changes have been observed in routine blood or urine examinations, nor in liver and kidney function tests. All tumors effectively stained yellow with FS during the surgical procedure. The senior neurosurgeon (N.F.) judged the use of YELLOW 560 nm filter, together with a low dose of FS as "helpful" in all cases. The resection extent was evaluated by two neurosurgeons and two neuroradiologists, by analyzing postoperative neuroimaging exams performed within 72 h after surgery (35 enhanced MRI, 12 enhanced CT scans). GTR was achieved in 53.2% (n = 25) of patients. A STR (>95%) was achieved in 29.8% (n = 14) of them, while a PR (<95%) was obtained in 17% (n = 8) of patients. Globally, a >95% resection was achieved in 83% (n = 39) of patients who underwent fluorescence-guided surgery. The median postoperative KPS score was 83.4 (range: 50–100). Postoperative score was higher for 15 patients, lower for 11, and was the same as the preoperative one for 21 patients. Overall, eight serious complications emerged: six postoperative brain hemorrhages, one sepsis, and one hydrocephalus. In fifteen patients, new motor deficits were observed after surgery, nine of which were transient paresis, which resolved completely within 1 month. In four patients seizures occurred postoperatively. There was no perioperative mortality. The overall median follow-up was 10.2 months (range: 3–18 months).

DISCUSSION

The importance of radical resection in glioma surgery has been already stressed in literature. Although rare cases of spontaneous regression of benign tumors after incomplete removal are described,[35] radical resection of malignant

tumor allows long-term survival.[15] Thus, the need for radical surgery in brain tumor is becoming a main stone of the modern neurosurgical philosophy. For this purpose, different technological excellences have been used in the operating theatres, as the new generation intraoperative neuroradiological assessment devices.[6] The use of fluorescent markers during surgical procedures to dye tumor tissue has become an important tool in neoplastic resection. Although the role of intraoperative contrast enhancement is well described in the literature, mainly for vascular diseases,[5] such a technique is progressively gaining more consent as a modern armamentarium to achieve radical removal. FS is a fluorophore, that has been used in medical applications for more than six decades.[25] This dye penetrates in those areas of the brain where the BBB is damaged, allowing real time enhancement of the areas enlightened by gadolinium in MRI. In experimental studies, a rodent BBB disruption with intra-arterial mannitol administration has been demonstrated to enhance fluorescein signal in the brain.[21] The fluorescence of FS can be grossly perceived to the naked eye, when this agent is injected at high doses (20 mg/kg). However, when using a recent developed microscope integrated YELLOW 560 module (Carl Zeiss Meditec, Oberkochen, Germany), we can employ a low dose of FS (5 mg/kg) to detect an optimal fluorescence within the tumoral tissue.[28] From the analysis of the literature [Table 4], it emerges that, besides its wide and safe use in ophthalmology,[20] fluorescein injection seems to be a good method to obtain a high rate of GTR during malignant brain tumors surgery.[26] The percentage of resection in the series that we have analyzed varied from 75% to 100%.[4] In 2003, Shinoda *et al.* reported a series of 32 patients surgically treated for glioblastoma multiforme. In 84.4% of these patients, gross total removal was obtained with a high dose of FS (20 mg/kg body weight). Only 30.1% obtained it with conventional white light imaging; no difference in the overall prognosis was observed in this series.[33] In 2008 Koc *et al.* reported a prospective nonrandomized study to evaluate the influence of FS-guided glioma resection on the extent of gross total tumor removal (GTR), overall prognosis, and side effects. Fourty-seven out of the 80 patients enrolled, received a high dose (20 mg/kg body weight) of intravenous FS after craniotomy. A standard operating room microscope without a filter or special camera was used. A second group of 33 patients underwent ordinary resections. The results showed a significant increase in the number of patients with GTR (83% vs. 55%) when fluorescein was administered. It was observed no statistically significant difference in overall survival between the two groups (44 weeks vs. 42 weeks).[16,20] In 2012 Chen, in a cohort of 22 patients with HGGs, observed a significant improvement in progression-free survival, together with the GTR rate, in patients treated with the aid of intraoperative intravenous injection of FS (15–20 mg/kg body weight) compared to the control group's progression-free survival.[8] In the same year, Okuda reported the safety and the efficacy of a new technique of fluorescence-guided surgery for GBM surgery based on high dose FS with excitation and barrier filters on the operating microscope (OME-9000 Olympus). This new technique was employed in a series of 10 patients, enabling a detailed tumor assessment and allowing the identification of tumor vessels and surrounding normal vessels. This dye allowed to perform the surgical removal with both fluorescence and under normal white xenon-light illumination.[27] After the study of Kuroiwa, who was the first to describe a novel technique of integration of the fluorescence filter in the microscope (Zeiss),[17] Schebesch in 2013 published data about a series of 35 patients with malignant brain tumor (whose 22 WHO HGGs) surgically treated with the aid of a reduced dose (3–4 mg/kg) of FS and with an intraoperative PENTERO 900 microscope equipped with the 560-nm wavelength fluorescence light filter. In all cases, the tissue fluorescence was brightly visible 30 min after administration of FS and it lasted for the entire duration of the procedure, representing a significant and "helpful" mean for the surgeon in 28 out of 35 cases.[31] Finally, Acerbi *et al.* was the first group to initiate a prospective phase II trial (FLUOGLIO) in 20 consecutive patients with HGGs. In these patients, FS was administered intravenously at the induction of anesthesia. In this case, the fluorescence visualization during the surgical procedure was obtained with BLUE 400 or YELLOW 560 filters on a PENTERO 900 microscope at a very low dose (10 mg/kg with the BLUE 400 filter and at 5 mg/kg with the YELLOW 560 filter). Data revealed a complete resection of the tumor in 80% of patients, a 6-months progression-free survival rate for 71.4%; moreover, a median survival of 11 months and a median duration of follow-up of 10 months were shown.[1-4] In February 2016, Hamamcıoğlu *et al.* presented their series of 23 high-grade tumors and seven metastatic tumors treated with the intraoperative aid of 200 mg (2–4 mg/kg) of FS. This dye was found

Table 4: Clinical series of patients with high-grade gliomas treated with a fluorescein sodium aided surgery. Literature review

Study	No. of HGG patients	FS dose	Gross total removal (%)
Shinoda *et al*. 2003[33]	32	20 mg/kg	84.4%
Koc *et al*. 2008[16]	47	20 mg/kg	83%
Chen *et al*. 2012[8]	22	20 mg/kg	80%
Okuda *et al*. 2012[27]	10	20 mg/kg	50%
Schebesch *et al*. 2013[31]	35	3-4 mg/kg	80%
Acerbi *et al*. 2013[3]	20	5 mg/kg	80%
Hamamcıoğlu *et al*. 2016[14]	23	2-4 mg/kg	79%

FS: Fluorescein sodium

"helpful" for tumor demarcation in 29 out of 30 operations (97%). In 23 of these 29 operations (79%), a total resection (radiologically demonstrated) was achieved regardless of the histopathology, whereas a near-total resection was achieved in four patients (14%). A STR was achieved in the remaining two patients (7%).[14]

In our experience, the use of FS together with YELLOW 560 nm filter has been found "helpful" in tumor removal in all the surgical procedures, allowing a better visual discrimination between the pinkish brain tissue and the yellow stained tumor tissue. This also seemed to be more comfortable to the surgeon eyes. The enhancement of tumoral tissue, which corresponds to the contrast enhancement of preoperative MRI, was visible immediately after dural opening, usually 30 min after the FS administration, and lasted until the end of tumor removal. The rate of tumor removal in our study was similar to that of previous studies. GTR was achieved in 53.2% (n = 25) of patients. A STR (>95%) was achieved in 29.8% (n = 14) of them, while a PR (<95%) was obtained in 17% (n = 8) of patients. Globally, a resection >95% was achieved in 83% (n = 39) of patients who underwent fluorescence-guided surgery. Moreover, FS seemed to be safe and effective in the intraoperative visual phase by distinguishing tumor from normal brain tissue and in the postoperative neuroimaging control. The resection was also maximized with the aid of neuronavigation system in eloquent areas, trying to avoid additional neurological deficit to the patient. The median postoperative KPS score was 83.4 (range: 50–100). Comparing pre- and postoperative scores, the latter was found higher in 15 patients, lower in 11, and stable in 21 patients. As in Schebesch, Acerbi, and Hamamcıoğlu series, we also report the use of low dose FS about 2 mL (5 mg/kg body weight). This low dose, together with YELLOW 560 nm filter, allowed an easier intraoperative management than higher doses of FS or 5-ALA, without the need to wait for the dye peak.[3,14,31] Although widely accepted in several fields of medicine as a very safe molecule, side effects of fluorescein administration, as skin reactions, syncope, respiratory or cardiac adverse effects, and seizures have been reported, but none of them occurred in this series.[17] Except for an expected and transitional change of skin color, sclera, and urine, which became slightly yellow (this effect disappeared completely within 24 h after fluorescein administration) none of the patients complained about any systemic or local side effect.[31] Although still limited by the small number of cases and by the absence of a control group of patients undergoing surgery without fluorescein (which we admit not to be a secondary aspect), our results are promising. It is clear that the use of intravenous fluorescein during the surgical removal of HGGs with a specific yellow filter, may be a very effective, safe, and inexpensive way to achieve a gross total removal of the tumor.[7] The cost of one application of 5-ALA is approximately 200 times higher than one administration of FS (approximately 980€ and 5€, respectively).[30] The use of specific filters on surgical microscope allows an optimal delineation of tumoral tissue, assuring the visualization of the fluorescent areas, and distinguishing them from the peritumoral brain parenchyma and from vessels, which appear of "more natural" colors.[4] It should be emphasized that fluorescence technology shows BBB breakdowns, corresponding to the areas marked by the contrast agent in MRI. Consequently, a resection based on FS fluorescence, allows the removal of those neural tissue portions in which the BBB is interrupted. It does not necessarily allow resection of the full extent of infiltrating tumor cells, thus potentially reducing the accuracy of tumor identification. Moreover, the necrotic portion of the tumor does not stain with fluorescein, due to its lack of cerebral vasculature.[2,10]

CONCLUSIONS

The intraoperative identification and resection of HGGs is a significant and important challenge in neurosurgery. In our series fluorescence-guided surgery of HGGs using FS has been a good tool in achieving GTR and in distinguishing tumoral by normal brain tissue. Larger-scale studies are now needed, to quantify the efficacy of fluorescein-guided surgery in improving the extent of resection as well as the progression-free and overall patient survival.

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There are no conflicts of interest.

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