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CLINICAL ARTICLE - NEUROSURGICAL TECHNIQUES

Fluorescence-guided surgery in high grade gliomas using an exoscope system

José Piquer Belloch · Vicente Rovira · Jose L. Llácer · Pedro A. Riesgo · Antonio Cremades

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Abstract
Background Fluorescence-guided microsurgical resections of high-grade gliomas using 5-aminolevulinic acid (5-ALA) is superior to conventional microsurgery. An optical device, usually a modified microscope, is needed for these procedures. However, an exoscope may be implemented for fluorescence techniques. We present the use of an exoscope to perform tumor resection guided by 5-ALA fluorescence in 21 consecutive patients with high-grade glioma and two neuronavigation-guided biopsies.
Methods Twenty-three patients underwent operations. Tumor volume and localization were quantified with pre- and post-operative volumetric MRI in non-biopsy cases.
Results In non-biopsy cases, the age range was 20 to 79 years, with a median of 56 (interquartile range=45-66). Histological analysis indicated that 14 had glioblastoma multiforme, 2 grade-III oligodendrogliomas and 1 anaplastic astrocytoma, 3 metastases and 1 low-grade astrocytoma. Total resection was achieved in 15 cases; subtotal resection was performed in 5 patients. The result was partial resection in one case. There was no perioperative mortality. The median fluorescence intensity, on a scale of 1–5, was 4.5 in the GBM group (IQR=4-5), 3 (IQR=2.5-3.5) in anaplastic glioma, and 2.5 (IQR=2.25-2.75) for oligodendrogliomas. Of the three metastases, one showed fluorescence level 4. As for the two biopsy cases, one was anaplastic astrocytoma and one glioblastoma multiforme. The samples obtained were fluorescent in both cases.
Conclusions An exoscope can be also used for fluorescence-guided surgery with 5-aminolevulinic acid (5-ALA) and neuronavigation-guided biopsy. With an important advantage of low cost, this allows the surgeon to perform collaborative surgeries and adds agility to the procedure.

Keywords High-grade glioma, glioblastoma · Aminolevulinic acid · Fluorescence

J. P. Belloch (✉) · V. Rovira · J. L. Llácer · P. A. Riesgo
Neurosurgery Service, Hospital de la Ribera, Carretera Corbera, 46600 Alzira, Valencia, Spain
e-mail: jose.piquer@telefonica.net

A. Cremades
Pathology Service, Hospital de la Ribera, Alzira, Spain

Introduction

High-grade gliomas account for 60–75 % of all gliomas. These represent the majority of adult malignant brain tumors and include grade III anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), mixed anaplastic oligoastrocytoma (AOA) and grade IV glioblastoma multiforme (GBM) [1].

Although still considered controversial by some authors [2–4], the current treatment of choice is extensive surgical resection, accompanied by chemotherapy and radiotherapy [4, 5]. Surgical tumor reduction has been shown to have an impact on both survival and quality of life [4, 6]. The grade of successful resection is directly related with the efficiency of complementary treatments; consequently, these should be as extensive as possible [2, 4]. There are also cases in which biopsy is the best option.

Because of the infiltrative nature of these tumors, complete resection is a complex neurosurgical procedure, regardless of the location of the lesion. Recent developments now allow multimodal approaches that have helped improve the neurosurgical technique, including brain mapping, neuronavigation, intraoperative ultrasound, magnetic resonance imaging, and fluorescence techniques [3, 7]. The benefits of fluorescence-guided surgery with 5-

aminolevulinic acid (5-ALA) for tumor resection of high-grade gliomas, particularly glioblastoma multiforme, have been shown in several reports [8–12]. 5-ALA fluorescence has been shown to have a high predictive value for the detection of tumor tissue and furthermore has the advantage of displaying it in real-time during surgery, thus increasing the percentage of patients in whom complete resection can be achieved, if no other considerations related to location and invasion of eloquent areas advise differently. Both neurosurgical microscopes and neuroendoscopes can be modified to detect the fluorescence induced by 5-ALA. This can be achieved by implementing a system to switch between white and blue light and installing an observation filter (440 nm) between the surgical field and microscope/endoscope. Most studies in 5-ALA-guided neurosurgery have been performed using fluorescence microscopy [8, 11, 13, 14] or, much less frequently, an endoscope [15]. However, to our knowledge, no studies have been published in which this technique was performed with an exoscope [16–18]. An exoscope system consists of a tubular telescope connected to a camera and a high-definition monitor. This method assists the surgeon by providing shared microscopic images of the surgical technique, thus allowing the performance of routine microsurgical procedures in a safe and minimally invasive environment, while the whole operating team has access to the images and the surgery can be recorded.

In this report, we describe our experience in the treatment of high-grade gliomas using 5-ALA-fluorescence-guided exoscopy, as an alternative or complement to the use of another optical device, in order to obtain the highest degree of tumor resection and, more recently, to confirm the adequacy of the biopsy specimen obtained.

Methods

This report includes the results of 21 patients with preoperative diagnosis of high-grade astrocytoma who were operated on at Hospital de la Ribera (Alzira, Spain) between January 2010 and October 2012. We also included two patients in whom neuronavigation-guided biopsy was performed. These procedures were carried out as normal clinical practice at our center and were approved by the Ethics Committee for Clinical Research of Alzira Hospital. The patients were fully informed about their clinical care and the exact procedures, indications and recommendations, and they gave their written consent, in accordance with Spanish law and the Declaration of Helsinki. Clinical and personal data were kept confidential.

The patients included were both male and female, >18 years of age, and initially diagnosed with high-grade glioma.

Preoperative procedures

Magnetic resonance imaging (MRI) was used for preoperative planning of tumor resection. A T1 sequence with contrast was used to obtain anatomical images, and the proximity of the tumor to eloquent areas was assessed by a functional MRI scan of areas close to the primary sensory or motor cortex and language area. A StealthStation® Surgical Navigation System (Medtronic, Inc., Minneapolis, MI, USA) was used for preoperative and intraoperative neuronavigation.

Neurophysiologic monitoring by transcranial or cortical stimulation for motor-evoked potentials was performed in two cases in which the tumor was close to primary motor areas. In one case the central groove was located by median nerve somatosensory-evoked potentials.

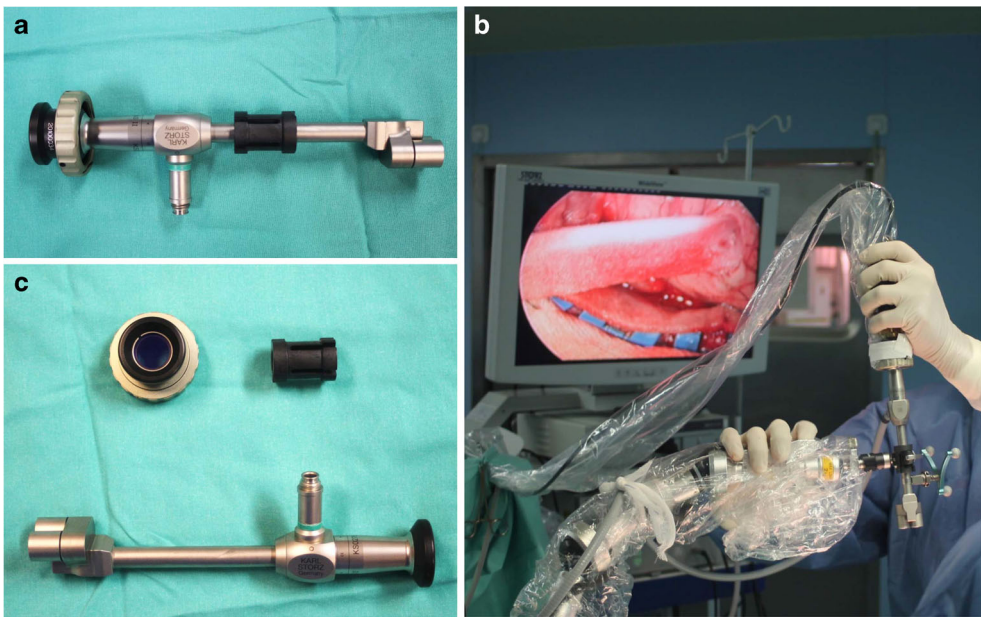

Fig. 1 General view of the exoscope setup. **a** Autoclavable rigid lens telescope; **b** Telescope held by pneumatic endoscope holder; **c** Threaded lens filter

Table 1 Clinical characteristics of cases included

No.	Age	HPD	ALA F	ALA I	Lobe	L*	Resection grade	2nd Sur	PND	Surgical Wound	Systemic CPL	SV	Presently
1	40 years	AA	No	4	Left frontal	B-1-1	Subtotal		No	No	PTE	11 months	Alive
2	50 years	GBM	No	4	Left frontal	B-0-1	Complete	Yes	No	Infection	No	17 months	Alive
3	61 years	GBM	No	5	Right parieto temporal	A-0-0	Complete		No	Infection	TCP	23 months	Alive
4	69 years	GBM	NO	4	Right parieto frontal	A-0-0	Partial		No	No	No	3 months	Deceased
5	43 years	GBM	No	5	Right temporal	A-0-0	Complete	Yes	No	No	No	19 months	Alive
6	59 years	GBM	No	2	Right frontal	A-0-0	Subtotal		No	No	No	11 months	Deceased
7	79 years	GBM	No	1	Right temporal	A-1-0	Complete		No	No	TCP PTE	2 weeks	Deceased (PTE)
8	28 years	OLG GIII	No	3	Right frontal	A-1-0	Complete		No	No	No	13 months	Alive
9	45 years	OLG GIII	No	2	Right frontal	A-1-0	Complete		No	No	No	12 months	Alive
10	50 years	AII	No	2	Left temporal	B-1-1	Partial		No	No	No	12 months	Alive
11	66 years	GBM	No	4	Right temporal	A-0-0	Complete		No	No	No	11 months	Alive
12	44 years	GBM	No	4	Left temporal	B-0-1	Complete		No	No	No	9 months	Deceased
13	55 years	GBM	No	5	Left temporal and corpus callosum	B-1-1	Subtotal		No	No	↑ GGT	9 months	Alive
14	56 years	GBM	No	5	Right parieto temporal	A-1-0	Complete	Yes	No	No	TCP	14 months	Alive
15	76 years	MET	Yes	1	Left temporal	B-1-1	Complete		No	No	No	6 months	Deceased
16	63 years	GBM	Yes	5	Right parietal	A-0-0	Complete		No	No	PTE	6 months	Alive
17	68 years	MET	Yes	4	Left frontal	B-1-1	Complete		↑Hemiparesia	No	No	3 months	Alive
18	20 years	GBM	Yes	5	Left parieto occipital	A-0-1	Complete		No	No	No	3 months	Alive
19	49 years	GBM	Yes	4	Right fronto temporal	A-1-0	Subtotal		Hemiparesia	No	No	5 months	Deceased
20	58 years	MET	Yes	1	Right frontal	A-0-1	Complete		↑Hemiparesia	No	No	2 months	Alive
21	66 years	GBM	Yes	5	Right temporal	A-1-0	Complete	Yes	No	No	No	12 months	Alive
22	69 years	AA	Yes	5	Left temporal and basal ganglia	C-0-1	Biopsy		No	No	No	2 months	Alive
23	76 years	GBM	Yes	5	Corpus callosum	C-0-1	Biopsy		No	No	No	2 months	Alive

HPD, histopathological diagnosis: AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; OLG,oligodendroglioma; G, grade, MET, metastasis; AII: astrocytoma grade II

I, intensity; F, filter L*: tumor location (Shinoda): location, size, andeloquence of adjacent parenchyma. SUR, surgery; PND, postoperative neurological deficit; CPL, complications; PTE, pulmonary thromboembolism; TCP, thrombocytopenia; SV, survival; GGT, gamma glutamyl transferase

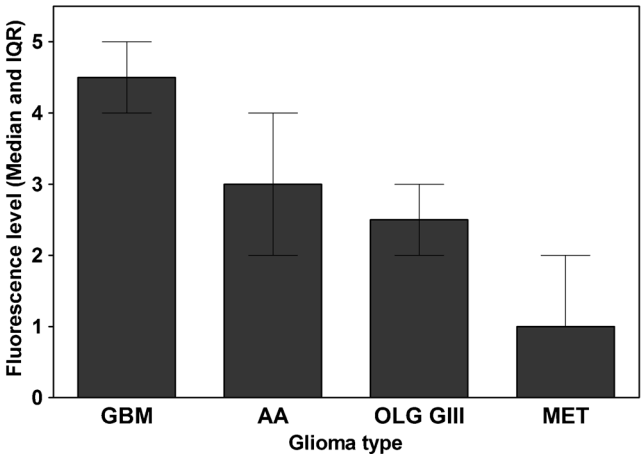

Fig. 2 5-ALA fluorescence intensities according to glioma type. The surgeon and the assistant graded the level of fluorescence of the solid tumor tissue on a 1–5 scale, 5 being the maximum level of 5-ALA fluorescence

All patients received 4 mg of dexamethasone three times daily for a minimum of 2 days before surgery.

Use of aminolevulinic acid

For 5-ALA administration, the detailed instructions in the product data sheet were followed (Gliolan®; Medac GmbH, Wedel, Germany). Briefly, 5-ALA, supplied in vials containing 1.5 g, is dissolved in 50 ml of drinking water (30 mg 5-ALA/1 ml of the reconstituted solution). The recommended dose of Gliolan® is 20 mg/kg, and the administered dose is weight-adjusted. Patients received a full dose of 5-ALA 3 h before surgery and were protected from strong light exposure within the first 24 h after 5-ALA administration to avoid risks related to photosensitivity.

Exoscope description and fluorescence guidance

Surgery was performed using a high-definition exoscope-assisted system (HD-Xoscope, HDXO-SCOPE, Karl Storz Endoscopy, Tuttlingen, Germany) [17, 18], including a specially developed autoclavable rigid lens telescope (Fig. 1a) and a fiber optic light source channel. The telescope is held in position by a pneumatic endoscope holder (Fig. 1b). The system is complemented with a 3-chip sterilizable high-definition digital camera with optical zoom and focus features and a video display with a medical grade 23" high-definition video monitor (2 million pixels). The technical characteristics of this kind of system have been described elsewhere [17, 18]. Image data are simultaneously sent to a data-archiving system.

Initially, the 5-ALA filter was a threaded lens filter positioned between the camera and the telescope (Fig. 1c). In the last nine cases, the filter was incorporated in the prototype. Therefore, this telescope/exoscope system was further implemented with a 5-ALA block filter, effectively blocking the excitation light while the fluorescence signal from the 5-ALA (380–450 nm) could pass through, along with normal white light. This design allows the filter to be already in position for the complete procedure needing white light and a rapid switch to a fluorescence signal when visualization of the tumor tissue that accumulated 5-ALA is needed. A pedal allows switching between white light and blue light, thus ensuring the appropriate visualization of fluorescent glial tumor tissue that accumulated 5-ALA.

Upon excitation with blue light (λ=400–410 nm), protoporphyrin IX, the 5-ALA metabolite accumulated in the tumor cells, is strongly fluorescent (peak λ=635 nm) and can be viewed in a specifically prepared neurosurgical optical system [19]. Fluorescence emission can be classified as intense (solid) red fluorescence, corresponding to tumor tissue (vital and solid), or faint pink or pinkish fluorescence, corresponding to infiltrating tumor cells. Normal tissue not accumulating protoporphyrin IX reflects the blue-violet light, appearing blue [20].

Surgical procedure and resection assessment

The general procedure consisted of routine craniotomy and the maximum tumor resection possible using neuronavigation, fluorescence of 5-ALA-induced protoporphyrin IX, and the appropriate fluorescence filter mounted in an exoscopy system. Resection was achieved by alternating white and blue light to complete exeresis, especially in areas marked red or pink. Resection was stopped when anatomical and neurophysiological references indicated that an eloquent area could be compromised. The surgical cavity was finally checked with blue light to confirm complete resection.

During surgery, several samples displaying different fluorescence intensities were obtained for tissue analysis. Fluorescence intensity was subjectively graded during surgery by both the surgeon and the assistant using a scale from 1 to 5 (5 being the highest intensity).

A MRI scan was performed in all of the craniotomy cases within the first 5 postoperative days to assess the extent of resection. The resonance study was performed with a T1 sequence and compared with the preoperative scan performed

Table2 Histopathological results correlated to fluorescence

	Fluorescence	
	Red	Blue
Case 16	Tumor	Necrosis
Case 18	Tumor	Tumor
Case 19	Tumor	Gliosis
Case 20	Tumor	Necrosis
Case 21	Tumor	Gliosis
Case 22	Tumor	Not tumor
Case 23	Tumor	Not tumor

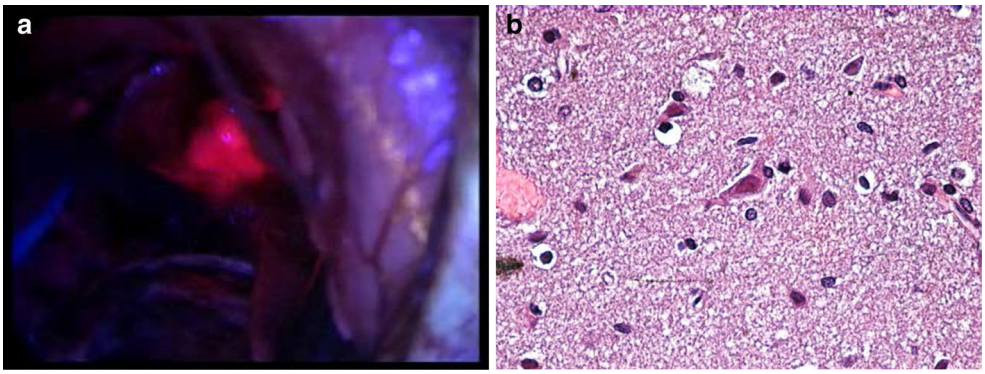

Fig. 3 Glioblastoma multiforme tumor area. **a** 5-ALA fluorescence image; **b** Histological analysis

the day before surgery. Complete resection was considered when exeresis involved≥95 % of initial volume, subtotal when the level of resection was between 85 and 95 %, and partial if less than 85 % of the malignant tissue could be extracted.

Results

Patient characteristics and the resection results are summarized in Table 1. Of the 21 patients in whom craniotomy was performed, 8 were female and 13 male. The age range was 20 to 79 years, with a median of 56 (interquartile range=45–66). All lesions were topographically classified according to Shinoda [21].

Assessment by MRI indicated that total resection was achieved in 15 cases, subtotal resection was performed in 5 patients, and in 1 case, the result was a partial resection. No complications or adverse reactions related to the administration of 5-ALA were observed, although a slight increase in serum GGT was found in one case, and two patients presented with thrombocytopenia, severe in one of them, who suffered pulmonary thromboembolism. Three cases of progression of hemiparesis after surgery were recorded, with subsequent partial recovery in two of them, and transient dysphasia was observed in one patient. There was no perioperative mortality.

Histopathological diagnosis of the lesions confirmed that our sample included 3 metastases and 18 high-grade gliomas: 14 patients had glioblastoma multiforme, 2 oligodendroglioma, and the remaining 2 had astrocytoma, 1 of low degree. Of the two biopsy cases, one was identified as anaplastic astrocytoma, and the other was glioblastoma multiforme.

The median fluorescence intensity, according to the subjective assessment of the surgeon and the assistant on a scale of 1–5, was 4.5 in the GBM group (IQR=4–5), 3 (IQR=2.5-3.5) in the cases of anaplastic glioma, and 2.5 (IQR=2.25-2.75) for the oligodendrogliomas (Fig. 2). Of the three metastases, one showed a level 4 degree of fluorescence. The histological analysis confirmed that the most fluorescent area corresponded to tumor tissue in the first 15 cases. The first 14 surgeries were performed without the 5-ALA filter adapted to the exoscope. In five of the seven craniotomy cases and in the two biopsy cases, operated on with the 5-ALA block filter, the technique was validated through histological correlation of presence or absence of tumor with the presence or absence of fluorescence: red or blue (Table 2). Tumor tissue or infiltration areas were easily identified by their bright red or pink color (Figs. 3 and 4), while non-tumor area reflected the blue light. The sample obtained from tumor tissue in both biopsies was fluorescent, indicating that the sample was good for histopathological diagnosis (Fig. 5). When positive fluorescence was observed at the surgical site or in the sample of

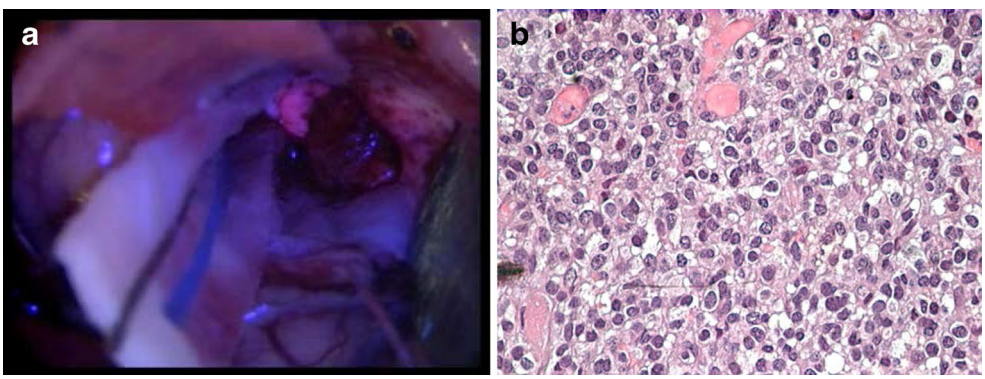

Fig. 4 Glioblastoma multiforme infiltration area. **a** 5-ALA fluorescence image; **b** histological analysis

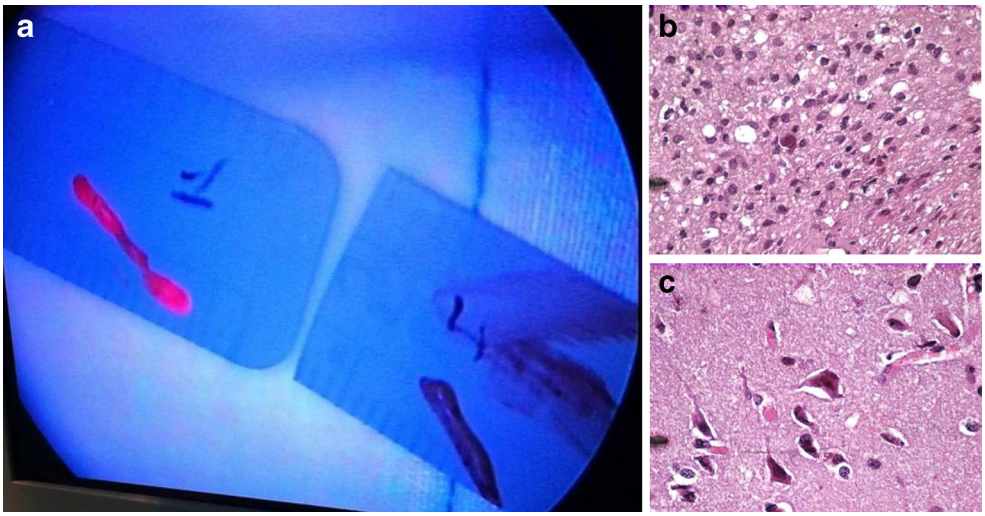

Fig. 5 Neuronavigation-guided biopsy. Samples obtained from tumor (1) and from peripheral area (4); **b** Histological analysis from 1; **c** histological analysis from 4

the seven cases, the existence of tumor was confirmed in all cases (100 %). When no fluorescence was observed (blue), in only four cases was the absence of tumor confirmed (57 %); however, of the remaining three cases, necrosis was observed in two, and only in one (14 %) was the existence of brain tissue with a small infiltrative tumor area revealed.

Discussion

Several studies have shown that fluorescence-guided tumor resection increases the rate of complete excision of high-grade glioblastomas, particularly in the case of glioblastoma multiforme, without significantly increasing morbidity [4, 10, 14, 19, 22–26]. 5-ALA fluorescence allows for tumor visualization in real-time during surgery, including diffuse infiltration areas in which tumor cells are mixed with normal parenchyma, so the malignant tissue can be easily identified [12, 20]. The pivotal study performed by Stummer et al. [11] on the use of 5-ALA fluorescence to guide the resection of high-grade gliomas using a microscope showed that complete resection was achieved in 65 % of patients treated with 5-ALA compared to 36 % of the untreated ones, a 6-month disease-free survival rate was achieved, and similar adverse effects between groups were found. In our study, of the 18 high-grade gliomas (14 GBM and 4 anaplastic gliomas), 70.5 % were completely excised, and the level of complications was similar to that in other reports, these results being very similar to those observed in larger series, though not statistically valuable in our small series.

There are no major difficulties in adapting a neurosurgical microscope or a neuroendoscope for detecting fluorescence induced by 5-ALA. Several kinds of commercial equipment come with this capacity, and this can also be achieved with the high-definition exoscope reported here. In the case of the equipment used in this series, the filter combination/specification is exactly the same as that used for surgical microscopes by other manufacturers. The electronic image was used with the settings specified by the manufacturer, since gain and shutter times have been evaluated and tested during the development of that system, and no modifications from the standard setting were used. In these conditions, the image obtained is similar to that obtained with a microscope. The difference between the endoscopic and exoscopic setups lies in the scope design and working distance. However, each device has its pros and cons. In the case of the endoscope, there is some experience in using this for fluorescent surgery [15], but it seems that its use has not spread, possibly because of the many limitations of this alternative. Among these is the diameter of the lens, which is usually very small, causing the focal distance to be very short. In our experience, this limits the ability to visualize fluorescence adequately, and the movement of the surgical instruments is hampered. Furthermore, the lens may be obscured with biological or other fluids during surgery. The most widespread instrument for this type of procedure is the surgical microscope. The field of vision in this case is large, as is the focal distance, providing a more ample working area for the surgical instruments. However, it also has its drawbacks. This device is heavy and expensive when compared with an exoscope, and depending on the equipment, manipulation can be cumbersome. In addition, high-quality microscopic images and the best lighting are offered only to the surgeon, and the optical pathway is split off for a second binocular system used by the assistant, not always facilitating collaborative work. The surgeon or the assistant may need to look at various angles that require uncomfortable positions for extended periods of time, possibly affecting the surgical outcome because of fatigue. Therefore, our group decided on the implementation of exoscope-aided neurosurgery and adapted this device for fluorescence procedures.

Since the first experiences in the use of a telescope adapted to a video system, the last 2 decades have seen a growing number of reports on the use of telescopic systems in various specialties such as general surgery, urology, gynecology, etc. [17, 27–30]. These high-definition systems have been described as allowing both the surgeon and assistant to work in an optimal position with an optimal working field. The advantages of this do not go unnoticed, as the system used in this study obtained high-quality images with a wide field and a target distance of 200 mm. This wide range allows the telescope to be arranged outside the surgical field, and the instruments can be used with fluoroscopy, which is impossible with traditional neuroendoscopes. We have observed that a microscopic exoscope has the advantage in areas such as price, weight, and handling. The size of the equipment allows portability and transfer to different hospitals. Furthermore, it can be sterilized, so the use of a sheath is not necessary. It also allows both the surgeon and assistant to adopt an ergonomic position, making it possible to perform surgery with "four hands" or to switch continuously from a microscopic to a macroscopic view during microsurgery, while the whole team has access to the images, a feature also appreciated by other surgeons [18]. Finally, the feature that allows the exoscope to be our alternative of choice is the circumstance addressed in the study: it can also accommodate a fluorescence filter and an ultraviolet light source along with a white light lamp, thus allowing fluorescence-guided surgery of glial tumors with high efficiency and security, and without the disadvantage of the assistant receiving less light than the neurosurgeon. Moreover, the system is an external telescope that remains outside the body cavity, thus providing the benefits of a microscope, such as an appropriate working field or minimal invasiveness, while being less bulky. It offers a large field of view with a long working distance and is easy to handle. In addition, a microscope is not needed for neuronavigation-guided biopsy, freeing up this resource for other procedures.

Conclusion

Our experience in this small series is that the fluorescence induced by 5-aminolevulinic acid can also be visualized with an exoscope system, allowing the surgeon to perform fully collaborative surgeries, to add agility to the procedure, and, if a biopsy has to be obtained, to ensure that the sample is valid for histopathological analysis. The exoscope has the advantages of lower price and portability, and allows working in an ergonomic position, thus minimizing fatigue and discomfort, which may negatively influence the surgical outcome. The combination of neuronavigation and 5-ALA fluorescence in this environment may contribute to optimal outcomes in the resection of high-grade gliomas.

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Conflict of Interest The authors declare no conflicts of interest in relation to the contents of this manuscript.

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