



Extending the Indications of 5-Aminolevulinic Acid for Fluorescence-Guided Surgery for Different Central Nervous System Tumors: A Series of 255 Cases in Latin America

Ampliando as indicações de ácido 5-aminolevulínico em cirurgia guiada por fluorescência para diferentes tumores do sistema nervoso central: Uma série de 255 casos na América Latina

Erasmus Barros da Silva Jr¹ Ricardo Ramina¹ Maurício Coelho Neto¹
Guilherme Augusto de Souza Machado¹ Marcella Santos Cavalcanti² Joseph Franklin Chenisz da Silva¹

¹Department of Neurosurgery, Section of Neuro-oncology, Instituto de Neurologia de Curitiba, Curitiba, Paraná, Brazil

²Department of Neuropathology, Instituto de Neurologia de Curitiba, Paraná, Brazil

Address for correspondence Erasmus Barros da Silva Jr, MD, MSc, Departamento de Neurocirurgia, Setor de Neuro-oncologia, Instituto de Neurologia de Curitiba, Rua Jeremias Maciel Perretto 300–Campo Comprido, Curitiba, Paraná, CEP: 81210-310, Brasil (e-mail: erasmo-inc@uol.com.br).

Arq Bras Neurocir 2022;41(1):e35–e42.

Abstract

Introduction Fluorescence guidance with 5-aminolevulinic acid (5-ALA) is a safe and reliable tool in total gross resection of intracranial tumors, especially malignant gliomas and cases of metastasis. In the present retrospective study, we have analyzed 5-ALA-induced fluorescence findings in different central nervous system (CNS) lesions to expand the indications of its use in differential diagnoses.

Objectives To describe the indications and results of 5-ALA fluorescence in a series of 255 cases.

Methods In 255 consecutive cases, we recorded age, gender, intraoperative 5-ALA fluorescence tumor response, and 5-ALA postresection status, as well the complications related to the method. Postresection was classified as ‘5-ALA free’ or ‘5-ALA residual’. The diagnosis of histopathological tumor was established according to the current classification of the World Health Organization (WHO).

Results There were 195 (76.4%) 5-ALA positive cases, 124 (63.5%) of whom underwent the ‘5-ALA free’ resection. The findings in the positive cases were: 135 gliomas of all grades; 19 meningiomas; 4 hemangioblastomas; 1 solitary fibrous tumor; 27 metastases; 2 diffuse large B cell lymphomas; 2 cases of radionecrosis; 1 inflammatory disease; 2 cases of gliosis; 1 cysticercosis; and 1 immunoglobulin G4-related disease.

Keywords

- ▶ 5-aminolevulinic acid
- ▶ brain cancer
- ▶ extent of resection

received
March 25, 2021
accepted
June 16, 2021
published online
January 4, 2022

DOI <https://doi.org/10.1055/s-0041-1739272>.
ISSN 0103-5355.

© 2022. Sociedade Brasileira de Neurocirurgia. All rights reserved. This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)
Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Conclusion Fluorescence with 5-ALA can be observed in lesions other than malignant gliomas or metastases, including meningiomas, hemangioblastomas, pilocytic astrocytomas, and lymphomas. Although there is need for further evidence for the use of 5-ALA beyond high-grade gliomas, it may be a safe and reliable tool to improve resection in positive tumors or to guide the histopathologic analysis in biopsies.

Introdução A fluorescência com ácido 5-aminolevulinico (5-ALA) é uma ferramenta segura e confiável para a ressecção total de tumores intracranianos, especialmente gliomas malignos e casos de metástase. Neste estudo retrospectivo, analisamos os achados de fluorescência induzida por 5-ALA em diferentes lesões do sistema nervoso central (SNC), visando ampliar as indicações de seu uso no diagnóstico diferencial.

Objetivos Descrever as indicações e resultados da fluorescência com 5-ALA em uma série de 255 casos.

Métodos Em 255 casos consecutivos, registramos idade, sexo, resposta tumoral de fluorescência intraoperatória com 5-ALA, e *status* de 5-ALA pós-ressecção, bem como as complicações relacionadas ao método. A pós-ressecção foi graduada como “5-ALA livre” ou “5-ALA residual”. O diagnóstico histopatológico foi estabelecido de acordo com a classificação atual da Organização Mundial de Saúde (OMS).

Resultados Houve 195 (76.4%) casos 5-ALA positivos, 124 (63,5%) dos quais foram submetidos a ressecção “5-ALA livre”. Os achados nos casos positivos foram: 135 gliomas; 19 meningiomas; 4 hemangioblastomas; 1 tumor fibroso solitário; 27 metástases; 2 linfomas difusos de grandes células B; 2 radionecroses; 1 doença inflamatória; 2 glioses; 1 cisticercose; e 1 doença relacionada à imunoglobulina G4.

Conclusões Fluorescência com 5-ALA pode ser observada em outras lesões além de gliomas malignos ou metástases, incluindo meningiomas, hemangioblastomas, astrocitomas pilocíticos, e linfomas. Embora haja necessidade de mais evidências para o uso de 5-ALA que não em casos de gliomas de alto grau, sua aplicação pode ser segura e confiável para melhorar a ressecção de tumores positivos ou orientar a análise histopatológica em biópsias.

Palavras-chave

- ▶ ácido 5-aminolevulinico
- ▶ câncer no cérebro
- ▶ extensão de ressecção

Introduction

5-aminolevulinic acid (5-ALA) is the sole precursor of the non-protein heme constituent of hemoglobin. Once biosynthesized, it is transformed in cytosol until it gets converted to protoporphyrin IX (PpIX) inside the mitochondria. The accumulation of PpIX in certain lesions helps to distinguish neoplastic from normal tissue under blue light filter for photodynamic detection.¹

Neurosurgical microscopes coupled with a switchable white and violet-blue light source excite the PpIX, enabling the visualization of tumor fluorescence, in red, and normal tissue, non-fluorescent, in blue.² Applications of 5-ALA in brain tumor surgery have been described in the last two decades, and have been stimulated by increasing resection areas with better progression-free survival (PFS), especially in malignant intracranial lesions, such as glioblastomas and metastases.³⁻⁵ These promising results evolved to distinct applications in recent laboratory and translational studies.⁶⁻¹¹ Over the years, 5-ALA has also been introduced in the treatment of other intracranial tumors,⁶⁻¹¹ especially in cases of metastases⁶⁻⁸ and meningiomas.⁹⁻¹¹

Routinely used in Europe, Asia and Australia, 5-ALA was approved by the United States Food and Drug Administration (FDA) in 2017.¹²⁻¹⁶ In Brazil, it is approved by the Brazilian Patent Office and National Sanitary Vigilance Agency (Agência Nacional de Vigilância Sanitária, ANVISA, in Portuguese) under registry number 80046190162.¹⁷

Since 2015, a few articles¹⁸⁻²⁰ have reported the initial Latin America experience with 5-ALA fluorescence brain surgery. This emerging tool has become standard to maximize brain tumor removal, enabling real-time guidance through the tissue with surgeon's constant interrogation about what is normal tissue and what is infiltrated brain. With other concomitant intraoperative tools, such as neuro-navigation, intraoperative magnetic resonance imaging (MRI), awake surgery, and electrophysiological monitoring, 5-ALA optimized the surgical treatment in neuro-oncology, providing safer and better outcomes.

The purpose of the present article is to describe the application of 5-ALA fluorescence-guided surgery to expand its indications beyond malignant gliomas and metastases.

Methods

Between November 2015 and May 2020, at our institution, there were 255 consecutive cases of central nervous system tumors in which the patients underwent 5-ALA fluorescence-guided surgery. All patients had a preoperative Karnofsky Performance Scale (KPS) > 70% at the time of the procedure. 5-aminolevulinic acid was administered in selected suspected cases of gliomas, metastases and meningiomas. The present study complies with ethical standards, and informed consent was obtained from patients or their relatives.

Preoperative Care

Every patient underwent an imaging evaluation with magnetic resonance imaging (MRI), spectroscopy, and perfusion. The indications for advanced MRI varied according to tumor location and diagnostic hypothesis. Tractography and functional MRI were performed for tumors in eloquent regions. Three hours prior surgery, 5-ALA was administered orally, amounting to a dose of 20 mg/kg dissolved in 50 mL of drinking water.

Intraoperative Care

Patient care (anesthesia induction, positioning etc.) was as routine. Intraoperative pathology were performed for every case. Image guidance with neuronavigation was used in all intracranial tumors. Electrophysiological stimulation and monitoring or awake surgery were also performed for tumors in eloquent areas. The OPMI PENTERO 800 (Carl Zeiss Meditec AG, Jena, Germany) was the neurosurgical microscope used in the present series.

During the craniotomy, switching from white to blue excitation light showed cortical and/or subcortical tumor infiltration and the limits of the 5-ALA positiveness. In cases of 5-ALA-negative tumors, intraoperative MRI (iMRI) was available. Fluorescence intraoperative findings were classified in three zones: non-fluorescent tissue – usually normal brain, necrosis, or 5-ALA negative tumors, in blue; strong 5-ALA fluorescence – in red, showing positive solid tumors; and poor 5-ALA fluorescence – in pink, showing infiltrating tissue. Intraoperative pathology examinations were performed in each fluorescent zone.

At the end of surgery, the cases in which all tissue with visible strong and poor fluorescence were classified as '5-ALA free'. Cases of residual tumors were classified as '5-ALA residual', and the decision was based on the risks of postoperative deficits. The final diagnosis was established according to the 2016 World Health Organization (WHO) criteria.

Postoperative Care

All patients underwent postoperative MRI scans in the first 24 hours. The imaging findings were evaluated by the neuro-radiology team.

Results

There were 255 cases in 236 patients ranging from 3 to 90 years of age who underwent 5-ALA fluorescence-guided

surgery. The sample was composed of 99 women and 137 men. A total of 19 patients with high-grade gliomas underwent surgery in two different occasions. ► **Table 1** summarizes the results based on the final diagnosis and the 5-ALA removal status. ► **Figs. 1 to 7** show illustrative cases of specific diseases.

Complications due to 5-ALA administration: one male patient with history of drug addiction presented cardiac arrhythmia two hours after the administration of 5-ALA, prior to anesthetic induction. Surgery was suspended and performed a week later, without additional administrations of 5-ALA. This case was excluded from the 5-ALA response results. No other complication associated with 5-ALA was found in the present series.

5-ALA response: there were 195 (76.4%) 5-ALA positive and 60 (23.6%) 5-ALA negative cases.

5-ALA removal status: 124 (63.5%) of the 195 positive cases underwent complete removal based on fluorescence ('5-ALA free'); in 57 (29.2%) cases, the patients underwent '5-ALA residual' resection; and there were 14 cases (7.3%) of biopsies with 5-ALA positivity.

Astrocytic and oligodendroglial tumors: there were 4 pilocytic astrocytomas: 2 (50%) negative and 2 (50%) positive for 5-ALA. Regarding diffuse tumors, there were 24 grade-II astrocytomas: 6 (25%) 5-ALA positive, 4 of which with heterogeneous fluorescence varying between poor and strong, and 18 (75%) 5-ALA negative; 7 oligodendrogliomas: 6 (85.7%) negative and 1 (14.3%) 5-ALA homogeneously positive. As for anaplastic tumors, there were 6 grade-III astrocytomas: 3 (50%) positive (in 2 of these cases, fluorescence was found in an anaplastic isle), and 3 (50%) negative; 10 anaplastic oligodendrogliomas: 9 (90%) positive (3 with heterogeneous fluorescence varying between poor and strong), and 1 (10%) negative. There were 108 glioblastomas: 4 (3.8%) negative, and 104 (96.2%) positive, 18 of which cases had heterogeneous fluorescence due to necrosis (negative) and positivity variation between poor and strong. Moreover, three (2.8%) cases 5-ALA positive glioblastomas were giant-cell variants.

Ependymal tumors: there were 3 grade-I subependymomas: 2 (66.6%) negative cases and 1 (33.4%) positive case; 8 grade-II ependymomas: 3 (37.5%) negative, and 5 (62.5%) positive (1 of which with heterogeneous fluorescence due to a subependymal component [poor] mixed with an ependymal [strong] component). There was one case of an anaplastic ependymoma that was positive.

Meningiomas: there were 17 cases of grade-I and 2 cases grade-II meningioma, all of them (100%) positive. In 2 (10.5%) of the cases, there was heterogenous fluorescence due to calcification zones (pink).

Mesenchymal non-meningothelial tumors: there were 4 hemangioblastomas and 1 solitary fibrous tumor, all of them positive.

Metastases: there were 35 cases, 8 (22.8%) negative, and 27 (77.2%) positive. There were 24 adenocarcinomas (10 in the lungs, 12 in the breasts, 1 in the thyroid, and 1 in the colon): 4 (16.6%) negative, and 20 (83.4%) positive; 5 melanomas: 3 (60%) negative, and 2 (40%) positive. There were 6

Table 1 Tumors classified by types, 5-aminolevulinic acid (5-ALA) response, and removal status

Diagnosis	Total	5-ALA positive	5-ALA removal
<i>Astrocytic and oligodendroglial</i>			
Pilocytic astrocytoma, grade I	4	2	2 5-ALA free
Difuse astrocytoma, grade II	24	6	4 5-ALA free
Oligodendroglioma, grade II	7	1	1 5-ALA free
Anaplastic astrocytoma, grade III	6	3	1 5-ALA free
Anaplastic oligodendroglioma, grade III	10	9	7 5-ALA free
Glioblastoma, grade IV	108	104	59 5-ALA free, 7 biopsies
Astroblastoma	1	1	1 5-ALA free
Diffuse midline glioma	1	1	1 biopsy
<i>Ependymal</i>			
Subependymoma, grade I	3	1	1 5-ALA free
Ependymoma, grade II	8	5	3 5-ALA free
Anaplastic ependymoma, grade III	1	1	1 5-ALA free
<i>Mixed neuronal-gliol</i>			
Ganglioglioma	4	0	–
Rosette-forming glioneuronal tumor	1	0	–
Dysplastic cerebellar gangliocytoma	1	0	–
<i>Meningiomas</i>			
Meningioma, grade I	17	17	16 5-ALA free
Atypical Meningioma, grade II	2	2	2 5-ALA free
<i>Mesenchymal non-meningothelial</i>			
Hemangioblastoma	4	4	4 5-ALA free
Solitary fibrous tumor	1	1	1 5-ALA free
<i>Metastatic</i>			
Adenocarcinoma, breast	10	6	4 5-ALA free
Adenocarcinoma, lung	12	12	7 5-ALA free/2 biopsies
Melanoma	5	2	2 5-ALA free
Small cells, kidney	2	1	1 5-ALA free
Adenocarcinoma, colon	1	1	1 5-ALA free
Adenocarcinoma, thyroid	1	1	1 5-ALA free
Adenoneuroendocrine carcinoma	3	3	1 5-ALA free/1 biopsy
Carcinoid tumor, lung	1	1	1 5-ALA free
<i>Other tumors</i>			
Diffuse large B-cell lymphoma	3	2	1 5-ALA free, 1 biopsy
Schwannoma	1	0	–
<i>Non-neoplastic</i>			
Radionecrosis	2	2	2 5-ALA residual
Inflammatory	2	1	1 5-ALA free
Gliosis	6	2	2 5-ALA residual, 1 biopsy
Cysticercosis	1	1	1 5-ALA free
Demyelinating disease	2	1	1 biopsy

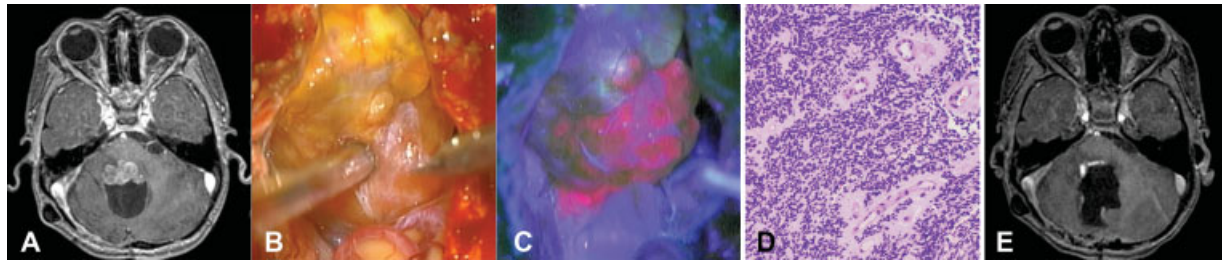


Fig. 1 Illustrative case of a grade-II ependymoma: (A) preoperative magnetic resonance imaging (MRI) scan; (B) intraoperative finding; (C) positivity for 5-aminolevulinic acid (5-ALA); (D) histopathological finding; (E) postoperative MRI.

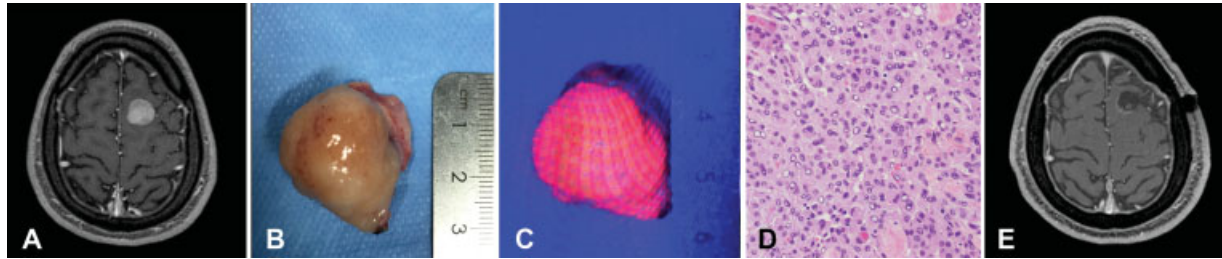


Fig. 2 Illustrative case of a grade-I meningioma: (A) preoperative MRI; (B) intraoperative finding; (C) 5-ALA positivity; (D) histopathological finding; (E) postoperative MRI.

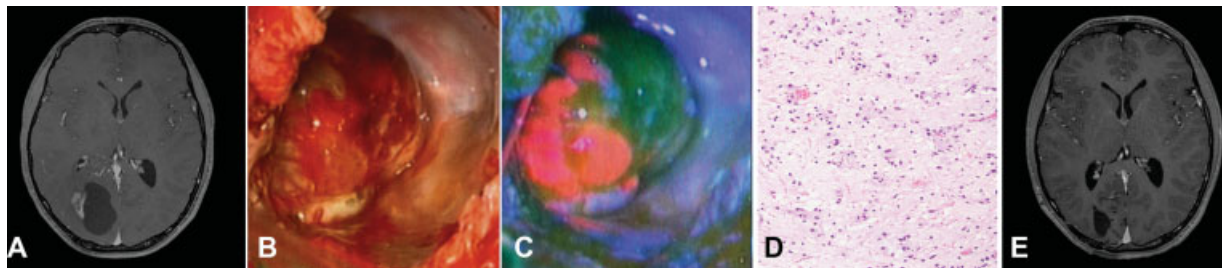


Fig. 3 Illustrative case of a pilocytic astrocytoma: (A) preoperative MRI; (B) intraoperative finding; (C) 5-ALA positivity; (D) histopathological finding; (E) postoperative MRI.

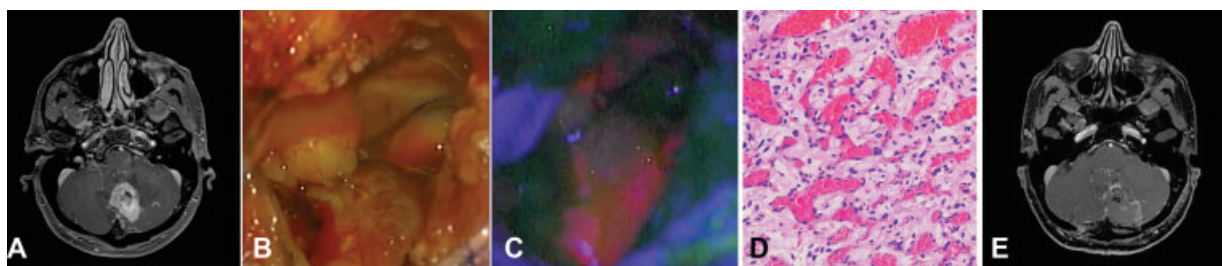


Fig. 4 Illustrative case of a hemangioblastoma: (A) preoperative MRI; (B) intraoperative finding; (C) 5-ALA positivity; (D) histopathological finding; (E) postoperative MRI.

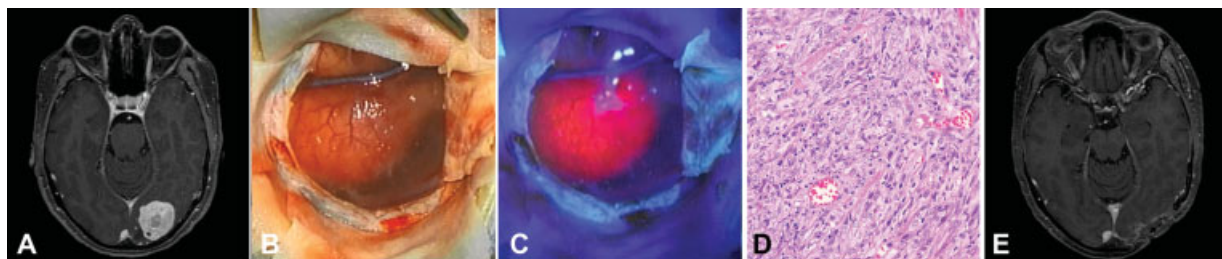


Fig. 5 Illustrative case of Solitary fibrous tumor: (A) preoperative MRI; (B) intraoperative finding; (C) 5-ALA positivity; (D) histopathological finding; (E) postoperative MRI.

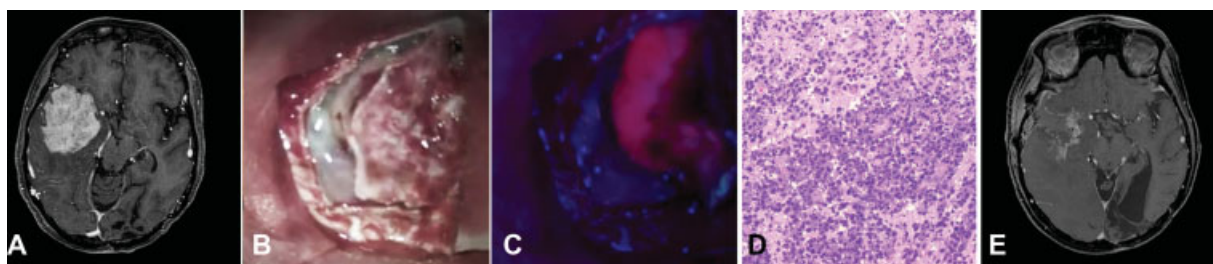


Fig. 6 Illustrative case of a diffuse large B-cell lymphoma: (A) preoperative MRI; (B) intraoperative finding; (C) 5-ALA positivity; (D) histopathological finding; (E) postoperative MRI.

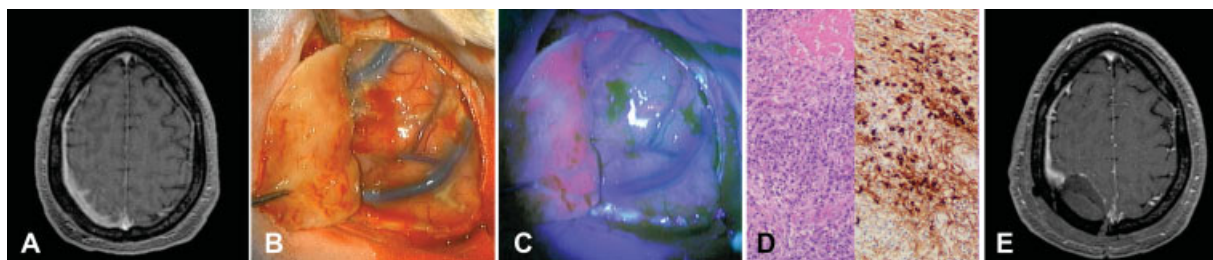


Fig. 7 Illustrative case of immunoglobulin G4-related disease: (A) preoperative MRI; (B) intraoperative finding; (C) 5-ALA positivity; (D) histopathological finding (left) with immunocytochemistry (right); (E) postoperative MRI.

other cases, which included 2 cases of small-cell carcinoma of the kidney (1 positive case and 1 negative), 1 carcinoid lung tumor, and 3 cases of mixed adeno-neuroendocrine carcinoma (all of them positive). Heterogeneous fluorescence varying from 'red to pink' was found in three (15%) adenocarcinomas.

Diffuse large B-cell lymphomas: 2 (66.7%) out of the 3 cases were positive, 1 of which had heterogeneous fluorescence varying between poor and strong.

Non-neoplastic diseases: there were 7 cases of unusual lesions; they were all positive, and included radionecrosis (2 cases with heterogeneous fluorescence), unspecific inflammatory disease (1 case), gliosis (2 cases with heterogeneous fluorescence), cysticercosis (1 case) and immunoglobulin G4-related disease (1 case, with pink fluorescence).

Discussion

A natural compound, 5-ALA is metabolized via the heme biosynthetic pathway to produce PpIX. Under fluorescent blue light, the PpIX stored in malignant lesions is distinguishable from normal brain tissue and enhances the intraoperative guidance for tumor removal. The intensity of the fluorescence predicts the degree of tumor cellularity.³⁻⁵ The optimal safe fluorescence was produced with 20 mg/kg by oral administration 4 to 6 hours prior to tumor removal. No fluorescence can be visualized with a dose of 0.2 mg/kg, and doses higher than 20 mg/kg do not enhance fluorescence.²¹

In 1998, Stummer et al.^{1,2} reported the first series of 270 cases of 5-ALA fluorescence-guided surgery for glioblastoma. In 2006, a randomized phase-III study confirmed 5-ALA as a reliable adjuvant tool to achieve gross total removal of high-grade gliomas, with a complete resection in 65% of 5-

ALA cases versus 36% of the patients who underwent conventional microsurgery;²² consequently, PFS was higher in the 5-ALA group.²³ In 2007, the European Medicines Agency (EMA) approved 5-ALA, but it was only approved by the FDA in 2017 for use as an intraoperative optical imaging agent in patients with suspected high-grade gliomas.¹² The delayed FDA approval was due to the conceptualization of 5-ALA as a therapeutic tool, not as an intraoperative imaging tool. Curiously, in 2004, Brazil's ANVISA approved 5-ALA as a dye to be applied on human subjects under registry number 80046190162.¹⁷

The first cases of 5-ALA fluorescence-guided surgery for intracranial tumors in Latin America were reported in 2018.^{18,19} Before that, neuronavigation, intraoperative MRI, and serial biopsy were the tools available to aid in maximal safe resections.²⁴ These techniques remain extremely relevant in cases in which fluorescence is negative.

Although the use of 5-ALA in the surgical resection of high-grade gliomas and cases of metastasis has been widely documented in the literature,⁶⁻¹¹ consistent findings of fluorescence have been reported regarding other tumors, including benign and non-neoplastic lesions.^{3,4} There are few available articles^{29,33,37} describing the use of 5-ALA fluorescence in those differential diagnoses.

For suspected low-grade gliomas or intra-axial tumors without contrast enhancement, the indication of 5-ALA fluorescence can be based on preoperative images suggesting anaplastic 'hot areas' on MRI perfusion. These anaplastic foci may be identified during resection by the accumulation of fluorescence and by a separate histopathological analysis. A shorter period may be expected for malignant transformation in patients with fluorescent low-grade gliomas.^{25,26} In the present article, 6 (25%) of the 24 confirmed cases of grade-II

astrocytoma, and 1 (14.2%) of the 7 cases of oligodendroglioma, were 5-ALA positive. These patients had a minimum follow-up of 2 years, and showed no signs of disease progression or differentiation until now. In contrast, of the 12 cases of 5-ALA positive grade-III astrocytic (3 cases) and oligodendroglioma (9 cases) lesions, 2 (16.6%) had their final diagnosis due to the finding of an anaplastic focus positive for 5-ALA. In both cases, there were preoperative images without contrast enhancement with hot spots on perfusion. The use of 5-ALA optimized tissue sampling for the histopathological evaluation. In the present series, the isocitrate dehydrogenase 1 (IDH1) status showed no relationship with 5-ALA positivity, corroborating the literature findings.²⁶

In high-grade gliomas, especially glioblastomas, 5-ALA fluorescence appears to be > 80% positive, with high sensitivity and positive predictive value.^{13,27} High-grade gliomas are the main and major indication for use of this method. In the present series, of 124 high-grade gliomas, 116 (93.6%) were 5-ALA positive, with 96.3% of glioblastomas and 75% of anaplastic gliomas. There were 42 (36.2%) cases of high-grade glioma that were '5-ALA residual' due to infiltration of eloquent areas. Previous adjuvant treatments, such as radiation and chemotherapy, in recurrent malignant tumors seem to not decrease the fluorescence response, although false-positive fluorescence can be observed more frequently.¹⁵ Of 19 cases submitted to reoperation with 5-ALA fluorescence, 2 (10.5%) presented radionecrosis despite heterogeneous positivity, ranging from negative to strongly positive zones.

There are few descriptions of 5-ALA fluorescence for pilocytic astrocytomas in pediatric patients, showing positivity in 53% of the cases.^{28,29} In the present series, 2 (50%) of 4 cases were 5-ALA positive, both appearing as a cystic mass with a mural nodule. Fluorescence was especially helpful in the final inspection for residual lesions.

Schwake et al.²⁹ described 71% and 80% of 5-ALA positivity in grade-III and -II ependymomas respectively. In the present study, out of 9 cases, 6 (66.7%) were positive, 1 of which was grade III. There was also 1 (33.3%) case in 3 of a 5-ALA positive subependymoma. Several articles³⁰⁻³² evaluated the utility of 5-ALA-guided removal of spinal lesions, finding positive fluorescence to be reliable especially in ependymomas and meningiomas.

In intracranial meningiomas, 5-ALA positive fluorescence may range from 77% to 96%,^{9,11} with intratumoral fluorescence homogeneity higher than 75%. In the present series, 100% of the 19 cases of meningioma were 5-ALA positive, with no apparent correlation with the histopathological grade. The method was useful to visualize dural and osseous infiltrations not visible under the white light of the microscope, previously described with 100% specificity and 89% sensitivity.¹⁰ This reinforces a possible benefit of 5-ALA in optimizing the resection result in conjunction with the Simpson removal classification. The long term follow-up of these patients will be the object of further studies.

Like pilocytic astrocytomas, hemangioblastomas can also show positive fluorescence in mural nodules.³³ 100% of the 4 cases described in the present article were 5-ALA positive, and the method helped achieve complete removal.

Large series^{6,7} of intracranial metastases show 5-ALA positivity ranging between 28% and 81.8%. In the present article, 77.2% of the cases were 5-ALA positive, with higher response in adenocarcinomas (83.3%) than in melanomas (40%). Fluorescence was useful to help define the possible cortical and subcortical limits of resection, although not necessarily containing metastatic infiltration.⁴ Heterogeneous positivity was found in 10 (28.5%) of the 5-ALA positive metastases, ranging from poor to strong fluorescent zones. Although expected in cases with previous adjuvant treatment such as chemotherapy and irradiation,⁶ we found no relationship in the present series. The use of 5-ALA was particularly efficient in cases in which 'en bloc' removal – in opposition to 'piecemeal resection' – was possible, given the possibility of safe oncological margins.

Due to the expected difficulty in the differential radiological diagnosis between high-grade glioma and primary central nervous system lymphoma, 5-ALA seems to be a useful tool in stereotaxic biopsies, optimizing tumor sampling based in positivity.^{34,35} In a series of 41 biopsies, Yamamoto et al.³⁶ observed 82.9% of 5-ALA positivity in primary central nervous system lymphomas. Evers et al.³⁷ reported 8 of 11 patients (73%) with strong homogenous fluorescence as well. In the present series, there were 14 5-ALA positive biopsies that aided in the intraoperative analysis. Samples were collected from both positive and negative areas. Intraoperative histopathology confirmed anomalous tissue in all positive fragments. It was especially helpful in non-neoplastic lesions, such as a case of immunoglobulin G4-related disease and an intracranial cysticercoid cyst.

In our experience, the use of 5-ALA has been safely extended to any contrast-enhanced tumor of the central nervous system, except for schwannomas. Its application to benign lesions such as pilocytic astrocytomas, hemangioblastomas, and meningiomas may have relevance in the final inspection of the surgical cavity, avoiding any residual fluorescence. Also, 5-ALA fluorescence seems to be especially interesting in atypical or challenging diagnoses, reinforcing its high sensitivity. These cases should be the subject of future studies.

Conclusion

Although more evidence is needed, the indications for 5-ALA fluorescence-guided surgery may be safely expanded based on the expected positive fluorescence. Its applications include tumors with potentially positive fluorescence other than malignant gliomas or metastases, optimizing removal and the histopathologic diagnosis.

Conflict of Interests

The authors have no conflict of interests to declare.

References

- 1 Stummer W, Stepp H, Möller G, Ehrhardt A, Leonhard M, Reulen HJ. Technical principles for protoporphyrin-IX-fluorescence guided microsurgical resection of malignant glioma tissue. *Acta Neurochir (Wien)* 1998;140(10):995-1000

- 2 Stummer W, Stocker S, Wagner S, et al. Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. *Neurosurgery* 1998;42(03):518–525, discussion 525–526
- 3 Ewelt C, Nemes A, Senner V, et al. Fluorescence in neurosurgery: Its diagnostic and therapeutic use. Review of the literature. *J Photochem Photobiol B* 2015;148:302–309
- 4 Ferraro N, Barbarite E, Albert TR, et al. The role of 5-aminolevulinic acid in brain tumor surgery: a systematic review. *Neurosurg Rev* 2016;39(04):545–555
- 5 Senders JT, Muskens IS, Schnoor R, et al. Agents for fluorescence-guided glioma surgery: a systematic review of preclinical and clinical results. *Acta Neurochir (Wien)* 2017;159(01):151–167
- 6 Kamp MA, Grosser P, Felsberg J, et al. 5-aminolevulinic acid (5-ALA)-induced fluorescence in intracerebral metastases: a retrospective study. *Acta Neurochir (Wien)* 2012;154(02):223–228, discussion 228
- 7 Kamp MA, Munoz-Bendix C, Mijderwijk HJ, et al. Is 5-ALA fluorescence of cerebral metastases a prognostic factor for local recurrence and overall survival? *J Neurooncol* 2019;141(03):547–553
- 8 Knipps J, Fischer I, Neumann LM, et al. Quantification of PpIX-fluorescence of cerebral metastases: a pilot study. *Clin Exp Metastasis* 2019;36(05):467–475
- 9 Millesi M, Kiesel B, Mischkulnig M, et al. Analysis of the surgical benefits of 5-ALA-induced fluorescence in intracranial meningiomas: experience in 204 meningiomas. *J Neurosurg* 2016;125(06):1408–1419
- 10 Rustemi O, Della Puppa A. Hyperostosis and osteolysis in skull base meningiomas: are different nuances of 5-ALA fluorescence related to different invasion patterns? *J Neurosurg Sci* 2019;63(04):484–485
- 11 Valdes PA, Millesi M, Widhalm G, Roberts DW. 5-aminolevulinic acid induced protoporphyrin IX (ALA-PpIX) fluorescence guidance in meningioma surgery. *J Neurooncol* 2019;141(03):555–565
- 12 Hadjipanayis CG, Stummer W. 5-ALA and FDA approval for glioma surgery. *J Neurooncol* 2019;141(03):479–486
- 13 Haider SA, Lim S, Kalkanis SN, Lee IY. The impact of 5-aminolevulinic acid on extent of resection in newly diagnosed high grade gliomas: a systematic review and single institutional experience. *J Neurooncol* 2019;141(03):507–515
- 14 Lakomkin N, Hadjipanayis CG. Fluorescence-guided surgery for high-grade gliomas. *J Surg Oncol* 2018;118(02):356–361
- 15 Chohan MO, Berger MS. 5-Aminolevulinic acid fluorescence guided surgery for recurrent high-grade gliomas. *J Neurooncol* 2019;141(03):517–522
- 16 Halani SH, Adamson DC. Clinical utility of 5-aminolevulinic acid HCl to better visualize and more completely remove gliomas. *OncoTargets Ther* 2016;9:5629–5642
- 17 Agência Nacional de Vigilância Sanitária Retificação de Publicação em Produtos para Saúde. Brasília, DF: Diário oficial da União; June 10, 2014. Suppl 109. 8419
- 18 Ramina R, Silva Júnior EB, Constanzo F, Coelho Neto M. Indications of 5-Aminolevulinic Acid and Intraoperative MRI in Glioma Surgery: First Cases in Latin America in a Single Reference Center. *Braz Neurosurg* 2018;37(02):88–94
- 19 Ramina R, Da Silva Júnior EB, Coelho Neto M, Ruschel L, Navarrette F. 5-Aminolevulinic Acid-Protoporphyrin IX Fluorescence-Guided Surgery for CNS Tumors. *J Bras Neurocir* 2018;27(01):13–19
- 20 Ruschel LG, Ramina R, da Silva EB Jr, Cavalcanti MS, Duarte JFS. 5-Aminolevulinic acid fluorescence-guided surgery for spinal cord melanoma metastasis: a technical note. *Acta Neurochir (Wien)* 2018;160(10):1905–1908
- 21 Stummer W, Stepp H, Wiestler OD, Pichlmeier U. Randomized, Prospective Double-Blinded Study Comparing 3 Different Doses of 5-Aminolevulinic Acid for Fluorescence-Guided Resections of Malignant Gliomas. *Neurosurgery* 2017;81(02):230–239
- 22 Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2006;7(05):392–401
- 23 Stummer W, Tonn JC, Mehdorn HM, et al; ALA-Glioma Study Group. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. *Clinical article. J Neurosurg* 2011;114(03):613–623
- 24 Ramina R, Coelho Neto M, Giacomelli A, et al. Optimizing costs of intraoperative magnetic resonance imaging. A series of 29 glioma cases. *Acta Neurochir (Wien)* 2010;152(01):27–33
- 25 Jaber M, Ewelt C, Wölfer J, et al. Is Visible Aminolevulinic Acid-Induced Fluorescence an Independent Biomarker for Prognosis in Histologically Confirmed (World Health Organization 2016) Low-Grade Gliomas? *Neurosurgery* 2019;84(06):1214–1224
- 26 Al-Tamimi YZ, Palin MS, Patankar T, et al. Low-Grade Glioma with Foci of Early Transformation Does Not Necessarily Require Adjuvant Therapy After Radical Surgical Resection. *World Neurosurg* 2018;110:e346–e354
- 27 Mansouri A, Mansouri S, Hachem LD, et al. The role of 5-aminolevulinic acid in enhancing surgery for high-grade glioma, its current boundaries, and future perspectives: A systematic review. *Cancer* 2016;122(16):2469–2478
- 28 Roth J, Constantini S. 5ALA in pediatric brain tumors is not routinely beneficial. *Childs Nerv Syst* 2017;33(05):787–792
- 29 Schwake M, Schipmann S, Mütter M, Köchling M, Brentrup A, Stummer W. 5-ALA fluorescence-guided surgery in pediatric brain tumors—a systematic review. *Acta Neurochir (Wien)* 2019;161(06):1099–1108
- 30 Eicker SO, Floeth FW, Kamp M, Steiger HJ, Hänggi D. The impact of fluorescence guidance on spinal intradural tumour surgery. *Eur Spine J* 2013;22(06):1394–1401
- 31 Millesi M, Kiesel B, Woehrer A, et al. Analysis of 5-aminolevulinic acid-induced fluorescence in 55 different spinal tumors. *Neurosurg Focus* 2014;36(02):1–11
- 32 Wainwright JV, Endo T, Cooper JB, Tominaga T, Schmidt MH. The role of 5-aminolevulinic acid in spinal tumor surgery: a review. *J Neurooncol* 2019;141(03):575–584
- 33 Utsuki S, Oka H, Sato K, Shimizu S, Suzuki K, Fujii K. Fluorescence diagnosis of tumor cells in hemangioblastoma cysts with 5-aminolevulinic acid. *J Neurosurg* 2010;112(01):130–132
- 34 Widhalm G, Minchev G, Woehrer A, et al. Strong 5-aminolevulinic acid-induced fluorescence is a novel intraoperative marker for representative tissue samples in stereotactic brain tumor biopsies. *Neurosurg Rev* 2012;35(03):381–391, discussion 391
- 35 Shooman D, Belli A, Grundy PL. Image-guided frameless stereotactic biopsy without intraoperative neuropathological examination. *J Neurosurg* 2010;113(02):170–178
- 36 Yamamoto T, Ishikawa E, Miki S, et al. Photodynamic Diagnosis Using 5-Aminolevulinic Acid in 41 Biopsies for Primary Central Nervous System Lymphoma. *Photochem Photobiol* 2015;91(06):1452–1457
- 37 Evers G, Kamp M, Warneke N, et al. 5-Aminolevulinic Acid-Induced Fluorescence in Primary Central Nervous System Lymphoma. *World Neurosurg* 2017;98:375–380