Use of fluorescence to guide resection or biopsy of primary brain tumors and brain metastases

*SERGE MARBACHER, M.D., M.Sc.,^{1,5} ELISABETH KLINGER, M.D.,² LUCIA SCHWYZER, M.D.,^{1,5}
INGEBORG FISCHER, M.D.,³ EDIN NEVZATI, M.D.,¹ MICHAEL DIEPERS, M.D.,^{2,5}
ULRICH ROELCKE, M.D.,^{4,5} ALI-REZA FATHI, M.D.,^{1,5} DANIEL COLUCCIA, M.D.,^{1,5}
AND JAVIER FANDINO, M.D.^{1,5}

Departments of ¹Neurosurgery, ²Neuroradiology, ³Pathology, and ⁴Neurology, and ⁵Brain Tumor Center, Kantonsspital Aarau, Aarau, Switzerland

Object. The accurate discrimination between tumor and normal tissue is crucial for determining how much to resect and therefore for the clinical outcome of patients with brain tumors. In recent years, guidance with 5-aminolevulinic acid (5-ALA)-induced intraoperative fluorescence has proven to be a useful surgical adjunct for gross-total resection of high-grade gliomas. The clinical utility of 5-ALA in resection of brain tumors other than glioblastomas has not yet been established. The authors assessed the frequency of positive 5-ALA fluorescence in a cohort of patients with primary brain tumors and metastases.

Methods. The authors conducted a single-center retrospective analysis of 531 patients with intracranial tumors treated by 5-ALA-guided resection or biopsy. They analyzed patient characteristics, preoperative and postoperative liver function test results, intraoperative tumor fluorescence, and histological data. They also screened discharge summaries for clinical adverse effects resulting from the administration of 5-ALA. Intraoperative qualitative 5-ALA fluorescence (none, mild, moderate, and strong) was documented by the surgeon and dichotomized into negative and positive fluorescence.

Results. A total of 458 cases qualified for final analysis. The highest percentage of 5-ALA-positive fluorescence in open resection was found in glioblastomas (96%, n = 99/103). Among other tumors, 5-ALA-positive fluorescence was detected in 88% (n = 21/32) of anaplastic gliomas (WHO Grade III), 40% (n = 8/19) of low-grade gliomas (WHO Grade II), no (n = 0/3) WHO Grade I gliomas, and 77% (n = 85/110) of meningiomas. Among metastases, the highest percentage of 5-ALA-positive fluorescence was detected in adenocarcinomas (48%, n = 13/27). Low rates or absence of positive fluorescence was found among pituitary adenomas (8%, n = 1/12) and schwannomas (0%, n = 0/7). Biopsies of high-grade primary brain tumors showed positive rates of fluorescence similar to those recorded for open resection. No clinical adverse effects associated with use of 5-ALA were observed. Only 1 patient had clinically silent transient elevation of liver enzymes.

Conclusions. Study findings suggest that the administration of 5-ALA as a surgical adjunct for resection and biopsy of primary brain tumors and brain metastases is safe. In light of the high rate of positive fluorescence in high-grade gliomas other than glioblastomas, meningiomas, and a variety of metastatic cancers, 5-ALA seems to be a promising tool for enhancing intraoperative identification of neoplastic tissue and optimizing the extent of resection. (<http://thejns.org/doi/abs/10.3171/2013.12.FOCUS13464>)

KEY WORDS • 5-ALA • protoporphyrin IX • Gliolan • fluorescence •
brain tumor • metastasis • biopsy

EXTENT of resection is an important prognostic factor that affects survival times for most patients with primary or secondary malignant brain tumors.^{22,23,34} However, during open tumor resection, it is often difficult to distinguish between normal brain and neoplastic tissue and to identify tumor margins,^{16,24,32} and during stereotactic biopsy of brain tumors, the sampling of positive pathological tissue specimens can be challenging.²⁵ For patients with glioblastoma (WHO Grade IV), the preop-

erative oral administration of 5-aminolevulinic acid (5-ALA) improves the intraoperative visualization of tumor with a blue-violet light source.^{30,38–40,45,49} For a series of patients with glioblastoma who underwent 5-ALA-guided tumor resection, radiologically confirmed complete resection rates of up to 83% were recently reported.⁶

A growing body of evidence indicates that the extent of tumor resection and therefore overall survival times for patients with glioblastoma can be positively influenced by 5-ALA fluorescence-guided surgery.^{30,39,45,49} In recent years, interest has increased in the assessment of 5-ALA as a promising intraoperative adjunct for detecting nonglioblastoma high-grade glioma, low-grade

Abbreviation used in this paper: 5-ALA = 5-aminolevulinic acid.
* Drs. Marbacher and Klinger contributed equally to this work.

glioma, and meningioma tissue.^{5,43,45} More recently, a retrospective study of 52 patients demonstrated that 62% of brain metastases were positive for intraoperative 5-ALA fluorescence.²⁰

Preliminary reports indicate that 5-ALA fluorescence increases the safety and accuracy of stereotactic and endoscopic brain biopsy procedures.^{25,31,47} It has been argued that speed and safety are increased by minimizing sampling errors.^{25,47}

Very few cases of adverse effects associated with use of 5-ALA during glioma surgery have been reported. In a series of 74 patients the authors described adverse events (phototoxic reaction, generalized edema) for only 2 patients.¹⁴ The authors of large approval studies among 500 patients receiving 5-ALA before glioma resection have reported no adverse events associated with the drug.^{37,39}

In this study, we analyzed our institutional experience with 458 consecutive cases of primary brain tumors and brain metastases treated either by microsurgical tumor resection or biopsy after oral administration of 5-ALA.

Methods

Patient Population and Data Acquisition

The study was supervised by the institutional review board of our institution, Kantonsspital Aarau. The off-label use of 5-ALA for intracranial tumors was approved by the Swiss Agency for Therapeutic Products (Swissmedic). Informed consent for surgical treatment and administration of 5-ALA (Gliolan, medac GmbH) was obtained for all patients.

From February 2007 through December 2011, a total of 531 patients underwent 5-ALA-guided open resection or biopsy of primary brain tumors or metastases at Kantonsspital Aarau. Of these, 458 patients fulfilled the following inclusion criteria: 1) age 18 years or older, 2) radiologically confirmed intracranial mass lesion, and 3) consensus to either operate or perform a biopsy after case review by the hospital's interdisciplinary neurooncology tumor board. Clinical data were collected from patient charts, surgical consent forms, operative reports and intraoperative video recordings, report forms on intraoperative 5-ALA fluorescence, histology reports, discharge summaries, and laboratory results.

The following characteristics were further analyzed: patient age, patient sex, histological diagnosis, tumor location, intraoperative 5-ALA fluorescence positivity, type of surgical procedure (open resection or biopsy), liver function test results (liver transaminases and γ -glutamyltransferase), and adverse reactions associated with administration of 5-ALA. The grading of intraoperative qualitative 5-ALA fluorescence (none, mild, moderate, and strong) was documented by the surgeon. Because this qualitative interpretation and grading of visible fluorescence is prone to interobserver bias, we therefore dichotomized all findings into negative (none) and positive (mild, moderate, and strong) fluorescence.

Clinical Management

All patients underwent preoperative MRI with a

standard examination protocol performed by a MAGNETOM Espree 1.5-T or a MAGNETOM Avanto 1.5-T scanner (Siemens). The protocol consisted of regular 5-mm diffusion-weighted imaging and susceptibility-weighted imaging sequences, a 4-mm T2-weighted turbo spin echo sequence (TR/TE 6080 msec/96 msec), a 6-mm T1-weighted spin echo sequence (TR/TE 450 msec/9.5 msec), and a true inversion recovery magnitude dark-fluid fat-saturated sequence (TR/TE 9000 msec/121 msec), each in axial planes. Additionally, a contrast-enhanced 0.9-mm T1-weighted volumetric interpolated breath-hold examination high-resolution sequence (TR/TE 6.2 msec/2.38 msec) was performed in a sagittal direction, with multiplanar reformat workups in 1-mm axial and coronal planes.

In accordance with the regulations of the European Medicines Agency (www.ema.europa.eu/), 5-ALA was administered only in the absence of any known history of liver disease and signs of significant hepatic dysfunction as seen clinically or determined by preoperative liver function tests. Further exclusion criteria for the administration of 5-ALA were history of photosensitivity, patient or family history of porphyria, or pregnancy. An aqueous solution of 5-ALA (Gliolan) was orally administered, at 20 mg/kg body weight, 3–5 hours before beginning the operation.

All open tumor resections were performed using standard microsurgical techniques and intraoperative neuronavigation tools (StealthStation Treon, Medtronic, or VectorVision, Brainlab AG). Tumor biopsy samples were obtained stereotactically using frameless neuronavigation systems (BrainPro Titanium Biopsy Cannula Set, PAJUNK GmbH) based on preoperative or intraoperative MRI scans (Polestar N20, Medtronic).

For evaluation of 5-ALA fluorescence positivity, blue-violet light was applied periodically during and at the end of tumor resection or after biopsy samples were obtained (440-nm blue-violet light source, OPMI Pentero, Carl Zeiss AG). To avoid phototoxic skin reactions from the sensitizing effect of protoporphyrin IX, patients remained in a dark environment for about 48 hours after surgery.^{9,21}

The formalin-fixed tissue specimens underwent standard histological evaluation with H & E staining and immunohistochemical analysis at our institution.

Postoperatively, we discussed all patients at our interdisciplinary neurooncology tumor board. Depending on age, histological result, WHO tumor grade, clinical condition, and performance status, patients either underwent treatment with standard protocols including radiotherapy with or without chemotherapy or they were observed with regular clinical and MRI follow-up assessments.

Results

A total of 531 5-ALA-guided microsurgical resections or biopsies of intracranial tumors were performed. Of those, 73 (14%) patients were excluded from the study, leaving 458 patients for final analysis. Reasons for exclusion were missing or conflicting (in terms of 5-ALA fluorescence) operative reports, intraoperative 5-ALA report

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forms, or video recordings (for 55 patients) or missing discharge reports (for 18 patients). Details on patient selection and clinical characteristics of the study population are presented in Fig. 1 and Table 1, respectively. All histological entities and their intraoperative 5-ALA fluorescence positivity are summarized in Table 2.

Intraoperative 5-ALA fluorescence was positive in 96% (n = 99/103) of glioblastomas, 83% (n = 5/6) of anaplastic oligodendrogliomas, and 82% (n = 14/17) of oligoastrocytomas (WHO Grade III) (Fig. 2). Compared with high-grade gliomas, there were only a small number of microsurgically resected low-grade gliomas (WHO Grades I and II) (Fig. 3). None of the WHO Grade I tumors (pilocytic astrocytoma, n = 0/2; ganglioglioma, n = 0/1) showed 5-ALA fluorescence. Fluorescence was positive in 42% (n = 5/12) of astrocytomas (WHO Grade II), 33% (n = 1/3) of oligoastrocytomas (WHO Grade II), and 100% (n = 2/2) of oligodendrogliomas (WHO Grade II).

Meningiomas formed the largest group of nonglial tumors resected in open surgery. In 77% (n = 85/110) of all meningiomas, 5-ALA fluorescence was positive (Fig. 4). Rates of fluorescence positivity were similar among WHO Grade I meningiomas (78%, n = 73/94) and WHO Grade II meningiomas (71%, n = 10/14).

Overall, positive 5-ALA fluorescence was documented for 52% (n = 34/65) of patients with brain metastases (Fig. 5). For further analysis, brain metastases were subdivided according to histology. Most metastases (n = 13/27) were adenocarcinomas. The primary sites of the adenocarcinomas were lungs for 5 patients, gastrointestinal tract for 7 patients (esophagus [n = 3], stomach [n = 1], and colon [n = 3]), and kidneys for 3 patients. 5-ALA fluorescence was positive in 86% (n = 6/7) of metastases from gastrointestinal adenocarcinomas but only 20% (n

= 1/5) of metastases from adenocarcinoma of the lung. In contrast, 5-ALA fluorescence was positive in 100% (n = 4/4) of metastases from small cell carcinomas of the lung. Other subtypes of metastases with high rates of positive 5-ALA fluorescence were invasive ductal carcinomas (no specific type) of the breast (71%, n = 5/7) and melanomas (76%, n = 3/4).

A total of 82 patients underwent stereotactic biopsy (Fig. 6). Of those, 5-ALA fluorescence was positive for 85% (n = 44/52) of high-grade gliomas (WHO Grades III and IV). A total of 6 biopsies from diffuse large B-cell lymphomas of the CNS were performed, of which 5-ALA fluorescence was positive for half (50%, n = 3/6).

No clinically apparent adverse effects associated with use of 5-ALA were observed. Postoperative liver function testing was performed only when liver dysfunction was suspected. For 1 female patient with postoperative abdominal discomfort, a moderate increase in liver enzymes was found and was graded as an adverse event (0.2%, n = 1/458). Antiedema therapy with corticosteroids was continued. The patient had no known liver disease or risk factors for liver dysfunction. Phototoxicity was not documented for any of the analyzed patients. However, because of the retrospective nature of the study, we cannot exclude the possibility that mild or temporary skin irritation occurred despite strict light protection.

Discussion

The results of this retrospective analysis of 458 patients demonstrate that 5-ALA is a safe surgical adjunct to open resection and biopsy of brain tumors. Apart from high-grade gliomas, rates of 5-ALA-positive fluorescence were high for a variety of other tumor entities. To

Fig. 1. Patient selection process. Asterisk indicates cases excluded because of missing data from source documents. Double asterisks indicate cases excluded because of missing or conflicting data concerning intraoperative 5-ALA fluorescence behavior.

TABLE 1: Clinical characteristics of 458 patients*

Characteristic	No. (%)
sex	
M	242 (52.8)
F	216 (47.2)
tumor etiology	
primary brain tumor	383 (83.6)
metastatic brain tumor	75 (16.4)
tumor location	
supratentorial	413 (90.2)
frontal	156
parietal	76
occipital	37
temporal	95
central region	12
insular	8
intraventricular	13
intrasellar/suprasellar	16
infratentorial	42 (9.2)
cerebellopontine angle	11
fourth ventricle	4
brainstem	11
cerebellar	13
clival	3
supratentorial & infratentorial	3 (0.7)
surgical procedure	
open resection	376 (82.1)
biopsy	82 (17.9)
adverse events associated w/ 5-ALA	1 (0.2)

* Patient mean age ($\pm$ SD) 59.1 $\pm$ 13.5 years; median 60 years, range 18–88 years.

the best of our knowledge, ours is the largest study of 5-ALA fluorescence behavior in nonglioblastoma lesions.

Molecular Mechanisms of 5-ALA–Induced Fluorescence

The hydrophilic 5-ALA is enzymatically converted to photosensitive protoporphyrin IX, which is transformed to heme after insertion of iron by the enzyme ferrochelatase.^{11,28} The detailed molecular mechanisms of selective accumulation in some tumor cells remain obscure. Several mechanisms have been hypothesized: altered activity of ferrochelatase, iron chelators, protoporphyrin IX synthesis, increased intracellular 5-ALA uptake, or disturbances in protoporphyrin IX outflow from malignant cells.^{4,8,29}

Given the hydrophilic nature of 5-ALA, disruption of the blood-brain barrier seems to be necessary for increased 5-ALA uptake into neoplastic brain lesions. Stummer et al. reported residual enhancement on MR images in 18 of 19 patients with residual intraoperative tissue fluorescence.³⁸ Recent data demonstrating a positive correlation between quantitative measurements of ex vivo protoporphyrin IX and gadolinium concentrations in patients undergoing fluorescence-guided glioma resec-

tion support the idea that blood-brain barrier breakdown is an important mechanism for increased intratumor protoporphyrin IX fluorescence.⁴⁶ Although significant, the correlation coefficient in the latter study was modest, and the authors concluded that additional factors probably play a key role in accumulated levels of protoporphyrin IX. Other factors, such as tumor tissue cell density and proliferation status in gliomas, are also strong predictors of protoporphyrin IX accumulation.⁴⁴

In meningioma tissue, tumor vascularization plays less of a role in intratumor 5-ALA accumulation. We recently demonstrated that meningioma fluorescence was not associated with preoperative steroid administration or peri-tumor edema.⁵

5-ALA Fluorescence in Primary Brain Tumors

Percentages of positive fluorescence in open resection were consistently high for high-grade gliomas (WHO Grades III and IV) (88%, $n = 122/138$) and biopsy (85%, $n = 44/52$). These findings are in line with reports in the literature of high rates of positive 5-ALA fluorescence in high-grade gliomas (glioblastomas, anaplastic oligoastrocytomas, and anaplastic oligodendrogliomas).⁴⁹

In our study, 5-ALA fluorescence was positive for 40% of low-grade gliomas (WHO Grades II). Recent studies investigating 5-ALA fluorescence in low-grade gliomas have shown positivity without use of any magnification in only 17% ($n = 1/6$) of patients,⁴⁴ whereas a positive rate of 100% ($n = 10/10$) could be demonstrated with the use of confocal microscopy.^{33,35} Ewelt et al.¹⁰ found 7.7% ($n = 1/13$) and Widhalm et al.⁴⁸ found no focal 5-ALA fluorescence in WHO Grade II tumors ($n = 0/8$). The authors of smaller series reported a lack of 5-ALA fluorescence in low-grade gliomas.^{14,17,42} These differences can be explained in part by the subjective nature and dichotomization of 5-ALA grading. In our series, even minimal fluorescence was characterized as fluorescent positive. Other possible explanations might be intratumor heterogeneity and sampling bias.

A possible explanation for the low rate of positive fluorescence might be that anaplastic astrocytomas, by definition, do not have endothelial proliferation, whereas anaplastic oligodendrogliomas and oligoastrocytomas frequently do. Therefore, we hypothesize that the main mechanism for the low rate of positive 5-ALA fluorescence in pure anaplastic astrocytomas compared with anaplastic oligoastrocytomas (WHO Grade III) and oligodendrogliomas (WHO Grade III) might be the result of disruption of the blood-brain barrier.^{2,3} It has been demonstrated that microvascular density correlates with concentrations of protoporphyrin IX in biopsy samples from gliomas.⁴⁶

5-ALA Fluorescence in Meningiomas

In recent years, the range for the use of intraoperative 5-ALA fluorescence has been extended to incorporate other non–high-grade primary brain tumors such as meningoepithelial tumors.^{1,5,7,26,27} In our series, 77% ($n = 85/110$) of meningiomas were 5-ALA fluorescence positive. In our previous series, 94% of 33 consecutive cases of meningioma demonstrated visible fluorescence.

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TABLE 2: Histological entities

Entity	No. of Cases (%)	
	5-ALA Positive	5-ALA Negative
primary brain tumors, open resection		
high-grade glioma (WHO Grades III–IV)	122 (88.4)	16 (11.6)
glioblastoma (WHO Grade IV)	99 (96.1)	4 (3.9)
oligodendroglioma (WHO Grade III)	5 (83.3)	1 (16.7)
oligoastrocytoma (WHO Grade III)	14 (82.4)	3 (17.6)
astrocytoma (WHO Grade III)	2 (22.2)	7 (77.8)
gliosarcoma (WHO Grade IV)	2 (66.7)	1 (33.3)
low-grade glioma (WHO Grades I–II)	8 (40.0)	12 (60.0)
oligodendroglioma (WHO Grade II)	2 (100)	0 (0)
oligoastrocytoma (WHO Grade II)	1 (33.3)	2 (66.7)
astrocytoma (WHO Grade II)	5 (41.7)	7 (58.3)
pilocytic astrocytoma (WHO Grade I)	0 (0)	2 (100)
ganglioglioma (WHO Grade I)	0 (0)	1 (100)
meningioma	85 (77.3)	25 (22.7)
WHO Grade I	73 (77.7)	21 (22.3)
WHO Grade II	10 (71.4)	4 (28.6)
WHO Grade III	2 (100)	0 (0)
pituitary adenoma	1 (8.3)	11 (91.7)
medulloblastoma	0 (0)	2 (100)
schwannoma	0 (0)	7 (100)
ependymoma	0 (0)	3 (100)
neurocytoma	0 (0)	1 (100)
hemangiopericytoma	1 (33.3)	2 (66.7)
hemangioma	0 (0)	2 (100)
gangliocytoma	0 (0)	1 (100)
chordoma	1 (50)	1 (50)
other	0 (0)	7 (100)
diffuse large B-cell lymphoma	2 (100)	0 (0)
brain metastases, open resection		
all metastases	34 (52.3)	31 (47.7)
adenocarcinoma	13 (48.1)	14 (51.8)
lung	1 (20)	4 (80)
prostate	0 (0)	1 (100)
esophagus	3 (100)	0 (0)
stomach	0 (0)	1 (100)
colon	3 (100)	0 (0)
kidney	2 (66.7)	1 (33.3)
urothelial carcinoma	1 (33.3)	2 (66.7)
small cell carcinoma of the lung	4 (100)	0 (0)
invasive ductal carcinoma (no specific type) of the breast	5 (71.4)	2 (28.6)
squamous cell carcinoma	1 (12.5)	7 (87.5)
melanoma	3 (75)	1 (25)
poorly differentiated carcinoma	3 (37.5)	5 (62.5)
endometrioid carcinoma	1 (100)	0 (0)
mucoepidermoid carcinoma	1 (100)	0 (0)
brain tumor, stereotactic biopsy		
high-grade glioma (WHO Grades III–IV)	44 (84.6)	8 (15.4)
glioblastoma (WHO Grade IV)	32 (88.9)	4 (11.1)

(continued)

TABLE 2: Histological entities (*continued*)

Entity	No. of Cases (%)	
	5-ALA Positive	5-ALA Negative
brain tumor, stereotactic biopsy (<i>continued</i>)		
high-grade glioma (WHO Grades III–IV) (<i>continued</i>)	44 (84.6)	8 (15.4)
oligoastrocytoma (WHO Grade III)	1 (50)	1 (50)
astrocytoma (WHO Grade III)	11 (78.6)	3 (21.4)
low-grade glioma (WHO Grades I–II)	3 (25)	9 (75)
oligoastrocytoma (WHO Grade II)	0 (0)	1 (100)
astrocytoma (WHO Grade II)	3 (30)	7 (70)
astrocytoma (WHO Grade I)	0 (0)	1 (100)
ependymoma	1 (100)	0 (0)
germinoma	2 (100)	0 (0)
multiple myeloma	0 (0)	1 (100)
gliomatosis cerebri	2 (66.7)	1 (33.3)
other	1 (33.3)	2 (66.7)
diffuse large B-cell lymphoma	3 (50)	3 (50)

A recent study of 15 patients reported 5-ALA positivity for 80% of meningioma cases.⁴³ The overall high rate of 5-ALA positivity suggests that 5-ALA could be a useful surgical adjunct, especially in the presence of ill-defined tumor margins (bone, dura, and brain parenchyma invasion), which is seen with some high-grade meningiomas.²⁶

5-ALA Fluorescence in Brain Metastases

Positive intraoperative 5-ALA fluorescence was documented in 52% (n = 34/65) of patients with brain metastases. With respect to 5-ALA fluorescence behavior, brain metastases form a heterogeneous group. Slightly higher rates of positive 5-ALA fluorescence have been reported in the literature. Kamp et al. reported positive fluorescence in 62% of metastases; 23 (70%) of 33 adenocarcinomas were positive.²⁰ In a series of 11 metastatic brain tumors, Utsuki et al. reported 5-ALA positivity for 82% of metastases.⁴¹

Also in our series, the rate of 5-ALA fluorescence

positivity in metastases from breast cancer was high (71%, n = 5/7). 5-ALA fluorescence was positive in only 1 of 4 urothelial carcinoma metastases. Published findings on intravesical instillation for the detection of transitional cell carcinoma indicate a detection rate of 92%.¹⁵ Although we have no true understanding for this pronounced difference in fluorescence positivity, possible explanations are as follows: the low number of urothelial carcinoma metastasis in our series (n = 4), the difference between biological behavior of the primary tumor and metastatic tissue, or the difference in 5-ALA administration (topical bladder instillation vs oral administration in our series). In a case series of 11 patients with breast cancer, all tissue samples from the primary tumor site were fluorescence positive.¹²

Use of 5-ALA in Stereotactic Biopsy of Brain Tumors

In their series on stereotactic brain tumor biopsy, von Campe et al. reported positive 5-ALA fluorescence in high-grade gliomas in all 13 patients.⁴⁷ In our series,

FIG. 2. Graph showing 5-ALA positivity in high-grade brain tumors. n indicates cases with positive fluorescence/total number of cases; black bars = 5-ALA-positive cases; white bars = 5-ALA-negative cases.

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Fig. 3. Graph demonstrating 5-ALA positivity in low-grade brain tumors. n indicates cases with positive fluorescence/total number of cases; black bars = 5-ALA-positive cases; white bars = 5-ALA-negative cases.

5-ALA fluorescence was positive in 84.6% (n = 44/52) of all biopsy samples from high-grade gliomas. On the basis of these data, we postulate that for patients with suspected high-grade glioma, the rate of negative collection of pathological tissue specimens in stereotactic biopsies can be reduced with the administration of 5-ALA.

Clinical Value of 5-ALA-Guided Resection of Primary Brain Tumors, Brain Metastases, and Biopsy of Patients With Suspected High-Grade Brain Tumors

The results of this study confirm high rates of 5-ALA-induced fluorescence in high-grade gliomas in general and in glioblastomas in particular. Intraoperative 5-ALA fluorescence was positive in 96% of glioblastomas and offered real-time in situ tumor identification, which enabled us to resect almost all neoplastic tissue in most cases. Although

we cannot make a definitive statement on the positive influence of 5-ALA on the extent of tumor resection, it is becoming increasingly difficult to ignore the fact that tumor fluorescence derived from 5-ALA enables more complete resection, which leads to improved progression-free survival times for patients with malignant glioma.^{30,39,45,49} In contrast, visible 5-ALA-induced fluorescence in low-grade gliomas (WHO Grade II) was rare, with only focal or vague fluorescence. In WHO Grade I tumors, 5-ALA fluorescence was absent. Therefore, it seems that visible 5-ALA fluorescence-guided surgery for low-grade gliomas (WHO Grade I and II) adds no value. We likewise found limited value for 5-ALA fluorescence-guided surgery for pituitary adenomas and schwannomas.

According to our observations, induced fluorescence in meningiomas is advantageous for visualizing menin-

Fig. 4. Graph showing 5-ALA positivity in meningiomas. n = cases with positive fluorescence/total number of cases; black bars = 5-ALA-positive cases; white bars = 5-ALA-negative cases.

FIG. 5. Graph demonstrating 5-ALA positivity in brain metastases. n indicates cases with positive fluorescence/total number of cases; black bars = 5-ALA-positive cases; white bars = 5-ALA-negative cases.

glioma tissue and defining the extent of resection in cases with bone, dural, or brain parenchyma invasion. These observations corroborate previous reports that after gross total tumor resection, remnants infiltrating the cortex are difficult to identify under white light inspection and may be visualized only under fluorescence.⁵ Furthermore, intraoperative photodynamic diagnosis provided by 5-ALA facilitates visualization of cranial bone infiltration,^{5,19,26} which constitutes an important factor for decreasing the risk for recurrence¹⁸ and associated poor outcome.¹³ Our study confirms the high rate of 5-ALA fluorescence in meningiomas and therefore highlights the usefulness of intraoperative fluorescence as a routine visual tool for achieving optimal resection.

With respect to their 5-ALA fluorescence behavior, brain metastases form a heterogeneous group; overall positive fluorescence rate was 52%. The rate of 5-ALA fluorescence was high for gastrointestinal adenocarcinomas (especially of the esophagus and colon), small-cell lung carcinomas, ductal carcinomas of the breast, and melanomas, and fluorescence provided valuable support for visualization of the brain-tumor interface. However, we infrequently observed intrametastatic 5-ALA fluorescence heterogeneity. Others have reported positive 5-ALA fluorescence in peri-tumor areas surrounding brain metastases.^{20,36,41} These reports and our own find-

ings indicate that more studies are needed to elucidate the potential role of 5-ALA in improving resection margins in various entities of brain metastasis.

We used 5-ALA fluorescence as an immediate intraoperative indicator of tumor tissue in patients undergoing diagnostic biopsy. In case of 5-ALA-positive sampling, frozen section confirmation was not requested, and the surgical procedure was completed. This approach did not result in any false-negative biopsy results in our case series and made the procedure faster and safer by reducing multiple biopsies and avoiding resampling in a substantial number of patients (67%). Our findings are consistent with those of von Campe et al., who found that all biopsy samples with positive fluorescence from patients with suspected high-grade gliomas were confirmed as neoplasms.⁴⁷

Conclusions

Our study confirms previous findings that, in addition to malignant gliomas, rates of positive 5-ALA fluorescence are high in certain brain metastases and meningiomas. In addition, this study shows that the administration of 5-ALA as a surgical adjunct for resection and biopsy of primary brain tumors and brain metastases seems to be safe. In light of the high rate of fluorescence positivity in

FIG. 6. Graph showing 5-ALA positivity in brain biopsies. n indicates cases with positive fluorescence/total number of cases; black bars = 5-ALA-positive cases; white bars = 5-ALA-negative cases.

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high-grade gliomas other than glioblastomas, meningiomas, and a variety of metastatic cancers, 5-ALA seems to be a promising tool for enhancing intraoperative identification of tumor tissue and therefore potentially optimizing the extent of resection.

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Disclosure

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Address correspondence to: Javier Fandino, M.D., c/o Editorial Office, Department of Neurosurgery, Kantonsspital Aarau, Aarau CH-5000, Switzerland. email: neurosurgery@ksa.ch.