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Editor's Choice

High Diagnostic Accuracy of Visible 5-ALA Fluorescence in Meningioma Surgery According to Histopathological Analysis of Tumor Bulk and Peritumoral Tissue

Lisa I. Wadiura, MD,[1,2] Matthias Millesi, MD,[1,2] Jessica Makolli, MD,[1] Jonathan Wais, MD,[1,2] Barbara Kiesel, MD,[1,2] Mario Mischkulnig, MD,[1,2] Petra A. Mercea, MD,[1,2] Thomas Roetzer, MD,[2,3] Engelbert Knosp, MD,[1,2] Karl Rössler, MD,[1,2] and Georg Widhalm, MD, PhD[1,2]*

[1]*Department of Neurosurgery, Medical University Vienna, Waehringer Gürtel 18-20, Vienna, 1090, Austria*
[2]*Comprehensive Cancer Center, Central Nervous System Tumours Unit (CCC-CNS), Medical University Vienna, Spitalgasse 23, BT86/E 01, Vienna, 1090, Austria*
[3]*Department of Neurology, Division of Neuropathology and Neurochemistry, Medical University of Vienna, Waehringer Gürtel 18-20, Vienna, 1090, Austria*

Background and Objectives: Complete neurosurgical resection of intracranial meningiomas is essential to avoid residual tumor tissue and thus minimize the risk of tumor recurrence. However, local recurrence of meningiomas is not uncommon mainly due to insufficient intraoperative detection of residual tumor tissue within the tumor bulk or peritumoral tissue such as bone and satellite lesions. Although 5-aminolevulinic acid (5-ALA) induced fluorescence was found to visualize the majority of meningiomas, no comprehensive histopathological assessment of fluorescing samples from the tumor bulk and peritumoral tissue is available. The aim of our study was thus to histopathologically analyze a large series of tissue samples derived from meningioma surgery to assess the positive predictive value (PPV) of visible 5-ALA fluorescence.

Study Design/Materials and Methods: In this study, we retrospectively investigated a series of tissue samples with visible 5-ALA fluorescence collected during surgery of intracranial meningiomas from the tumor bulk and peritumoral tissue including the bone flap, dura/dural tail, arachnoidea, adjacent cortex, and satellite lesions. The tumor diagnosis was established according to the World Health Organization (WHO) criteria and all collected fluorescing samples were screened for presence of tumor tissue to calculate the PPV.

Results: Altogether, 191 tissue samples with visible 5-ALA fluorescence derived during surgery of 85 meningiomas (63 WHO grade I, 17 WHO grade II, and 5 WHO grade III) were included. In detail, 158 samples from the tumor bulk and 33 specimens from the peritumoral tissue were investigated. According to histopathological analysis, the PPV of 5-ALA fluorescence was significantly higher in samples from the tumor bulk (100%) as compared with peritumoral tissue (73%; $P < 0.001$). With regard to peritumoral tissue, tumor tissue was present in most fluorescing samples from the satellite lesions (100%), the bone flap (92%), arachnoidea (83%), and dura/dural tail (75%). In contrast, tumor tissue was absent in the majority of samples from fluorescing cortex (six of seven samples; 86%). However, distinct reactive tissue alterations were found in all six tumor-free fluorescing cortex samples and additional vascular proliferation in two cases.

Conclusion: In this largest series to date, visible 5-ALA fluorescence is characterized by a high PPV detecting tumor bulk and peritumoral tissue in intracranial meningiomas. Thus, 5-ALA fluorescence supports the neurosurgeon in identifying residual tumor tissue at relevant surgical sites to optimize meningioma surgery and minimize the risk of local recurrence. © 2020 The Authors. *Lasers in Surgery and Medicine* published by Wiley Periodicals LLC

Key words: 5-ALA; fluorescence; meningioma; histopathology; tumor bulk; peritumoral tissue

INTRODUCTION

Intracranial meningiomas constitute the most common benign brain tumors in adults and account for approximately 30% of all primary central nervous system neoplasms [1]. Generally, surgical resection represents the treatment of choice in patients suffering from intracranial meningiomas. The goal of surgery is complete neurosurgical

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*Correspondence to: Georg Widhalm, MD, PhD, Department of Neurosurgery, Medical University Vienna, Waehringer Guertel 18-20, A-1097 Vienna, Austria. E-mail: georg.widhalm@meduniwien.ac.at

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resection to minimize the risk of local tumor recurrence. Nevertheless, local recurrence is not uncommon, even in World Health Organization (WHO) grade I meningiomas, despite assumed complete resection [2–4]. Aside from high-grade meningioma (WHO II and III) histology, residual tumor tissue that remains undetected during resection of intracranial meningiomas is a crucial factor for local tumor recurrence. Such residual meningioma tissue might be localized in the tumor bulk as well as peritumoral tissue such as the bone flap, dura/dural tail, arachnoidea, adjacent cortex, or satellite lesions.

Nowadays, improved visualization of residual tumor tissue with assistance of 5-aminolevulinic acid (5-ALA) fluorescence has been established as a powerful technique during surgery of high-grade gliomas (HGG) [5–7]. Recently, 5-ALA fluorescence was also applied in other tumors than HGG for improved intraoperative identification of anaplastic foci, various tumors in stereotactic biopsies, spinal tumors, brain metastases and meningiomas [8–15]. In meningiomas, visible 5-ALA fluorescence of the tumor bulk during meningioma surgery was reported in a recent series in 77–94% of patients [14–16]. According to first observations, 5-ALA fluorescence was found to be useful to visualize also peritumoral tissue such as infiltrated bone flaps and satellite lesions [14]. Although visible 5-ALA fluorescence was observed in the majority of meningiomas, no comprehensive histopathological assessment of fluorescing samples from the tumor bulk and peritumoral tissue is available in a large patient series. These data would be crucial optimizing meningioma surgery to minimize the risk of local tumor recurrence.

The aim of this retrospective study was thus to investigate the positive predictive value (PPV) of visible 5-ALA fluorescence in intracranial meningiomas. For this purpose, we analyzed the histopathological correlate of a large cohort of fluorescing samples from the tumor bulk and peritumoral tissue collected during meningioma surgery.

METHODS

In this retrospective study, adult patients (≥18 years) that underwent resection of a histopathologically confirmed intracranial meningioma (WHO grade I–III) after 5-ALA administration and available tissue samples from areas with visible fluorescence for histopathological analysis were included. All patients were surgically treated at the Department of Neurosurgery of the Medical University, Vienna (MUV) between 2009 and 2018. This retrospective study was approved by the local ethics committee of the MUV (*EC no.: 419/2008, amendment*).

Preoperative Imaging

A diagnostic magnetic resonance imaging (MRI) with contrast media application was preoperatively conducted in each patient. In addition, contrast-enhanced T1-weighted images were generally acquired for integration of these images into neuronavigation. If tumor infiltration of the bone flap was suspected on preoperative MRI, we additionally performed a computerized tomography. The tumor localization was categorized into seven main localizations consisting of the convexity, anterior cranial fossa, middle cranial fossa, posterior cranial fossa, falx, tentorium, and intraventricular region.

Neurosurgical Meningioma Resection After 5-ALA Administration

In each patient, 5-ALA (20 mg/kg bodyweight) was orally administered approximately 3 hours before anesthesia. At our department, we routinely perform resection of intracranial meningiomas with assistance of neuronavigation. During surgeries with prior 5-ALA administration, we use a modified neurosurgical microscope (NC4 or Pentero, Carl Zeiss Surgical GmbH, Oberkochen, Germany) for intraoperative visualization of potential fluorescence as described previously [17]. Generally, tissue samples were collected, if this was safely possible, from tumor suspicious areas with visible 5-ALA fluorescence within the tumor bulk and/or peritumoral tissue particularly the bone flap, dura/dural tail, arachnoidea and satellite lesions according to the surgeons preference. At our center, collection of tissue samples from the adjacent cortex is performed only in exceptional cases with clear intraoperative suspicion of tumor infiltration and if this can be safely performed. In this study, we screened the neuropathology reports for tissue samples collected during meningioma surgery after 5-ALA administration with available information on the visible 5-ALA fluorescence status (visible or no fluorescence) and the corresponding tissue for histopathological analysis.

Postoperative Course and Histopathology

After oral administration of 5-ALA, all patients were routinely protected from strong light sources for at least 24 hours to avoid potential skin phototoxicity. Tumor diagnosis was established according to the valid histopathological WHO criteria available at the time of diagnosis and only meningiomas (WHO grade I–III) were included in this study [18,19]. Each fluorescing sample was screened for the presence of tumor tissue (tumor or no tumor tissue). All significant side effects after administration of 5-ALA and further clinical data were retrieved from our database and the patient's records.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software (Version 24.0; SPSS Inc. [Armonk, NY, IBM Corp.]). General statistical characterization of the patient cohort included age, sex, WHO grade, tumor localization, and recurrent tumor surgery. The collected tissue samples were subsequently stratified by origin from the tumor bulk versus peritumoral tissue and PPV were determined for the entire cohort as well as for these subgroups. Inferential statistical testing was performed to test for a difference in likelihood of histopathological proof of tumor cells between fluorescent specimens obtained from tumor bulk and non-tumor bulk using χ^2 test. A $P < 0.05$ was considered statistically significant.

RESULTS

In this study, 81 patients with surgery of a histopathologically confirmed intracranial meningioma after 5-ALA administration were included. In none of the included patients any significant side effects related to the 5-ALA administration were observed in the perioperative course.

Patient Characteristics

The median age of this study cohort was 59 years (range 24–88 years) with a female to male ratio of 2:1. In the 81 patients, 85 tumors including 63 (74%) WHO grade I meningiomas, 17 (20%) WHO grade II meningiomas, and 5 (6%) WHO grade III meningioma were surgically removed. In detail, three patients with an atypical meningioma (WHO grade II) had an additional surgery due to local tumor recurrence. In the remaining patient with an anaplastic meningioma (WHO grade III), a second surgery was performed due to an additional meningioma at another tumor localization than the primary surgical site. The two most common tumor localizations were the convexity in 36 (43%) cases and the anterior cranial fossa in 26 (31%) cases. Further details are provided in Table 1.

TABLE 1. Patient Characteristics

		n	%
Number of patients		81	(100)
Gender	Female:male	2:1	
Age	Median (range)	59 years (24–88)	
Number of meningiomas		85	(100)
Recurrent meningioma			
No		64	(75)
Yes		21	(25)
Tumor localization			
Convexity		36	(43)
Anterior cranial fossa		26	(31)
Middle cranial fossa		8	(9)
Falx		7	(8)
Posterior cranial fossa		6	(8)
Intraventricular		1	(1)
WHO grade			
I		63	(74)
II		17	(20)
III		5	(6)
Simpson grade			
I		51	(60)
II		15	(18)
III		12	(14)
IV		7	(8)
V		0	(0)

WHO, World Health Organization.

Localization of the Collected Fluorescing Tissue Samples

Altogether, 191 tissue samples with visible fluorescence from surgery of 85 meningiomas were included in the current analysis. With regard to the localization of tissue collection, 158 (83%) of 191 samples were derived from the tumor bulk, whereas 33 (17%) of 191 samples were classified as peritumoral tissue. The 33 samples from peritumoral tissue were collected in 25 patients with a maximum of two samples per patient. In detail, in the majority of patients ($n = 17$) one tissue sample from the peritumoral tissue and in the remaining patients ($n = 8$) two samples were collected. Of the 33 fluorescing samples from peritumoral tissue, 12 (36%) specimens were collected from suspected bone flap infiltration, 7 (21%) specimens from adjacent cortex, 6 (19%) specimens from arachnoidea, and 4 (12%) specimens from the dura/dural tail as well as from satellite lesions distant to the main meningioma bulk, respectively. More details are given in Table 2.

5-ALA Fluorescence and Histopathology

According to histopathological analysis, presence of tumor tissue was found in 182 (95%) of all 191 fluorescing tissue samples. In contrast, no tumor cells were present in the remaining 9 (5%) tissue samples despite the presence of fluorescence.

Fluorescing tumor bulk tissue. With regard to the localization of tissue collection, tumor tissue was present in all 158 (100%) tumor bulk samples with visible fluorescence. Thus, the PPV of visible fluorescence for detecting tumor tissue was 100% in the group of 158 tumor bulk samples. See also Figure 1.

Fluorescing peritumoral tissue. In the group of fluorescing samples from peritumoral tissue, the presence of tumor tissue was confirmed by histopathology in 24

TABLE 2. Characteristics of Fluorescing Tissue Samples

	n	%
Number of 5-ALA + samples	191	(100)
Number of 5-ALA + samples per tumor		
1	41	(48)
2	17	(20)
3	12	(14)
4	4	(5)
≥5	11	(13)
Tumor bulk	158	(83)
Peritumoral tissue	33	(17)
Bone flap	12	(36)
Cortex	7	(21)
Arachnoidea	6	(19)
Dura/dural tail	4	(12)
Satellite lesion	4	(12)

5-ALA+, 5-aminolevulinic acid positive.

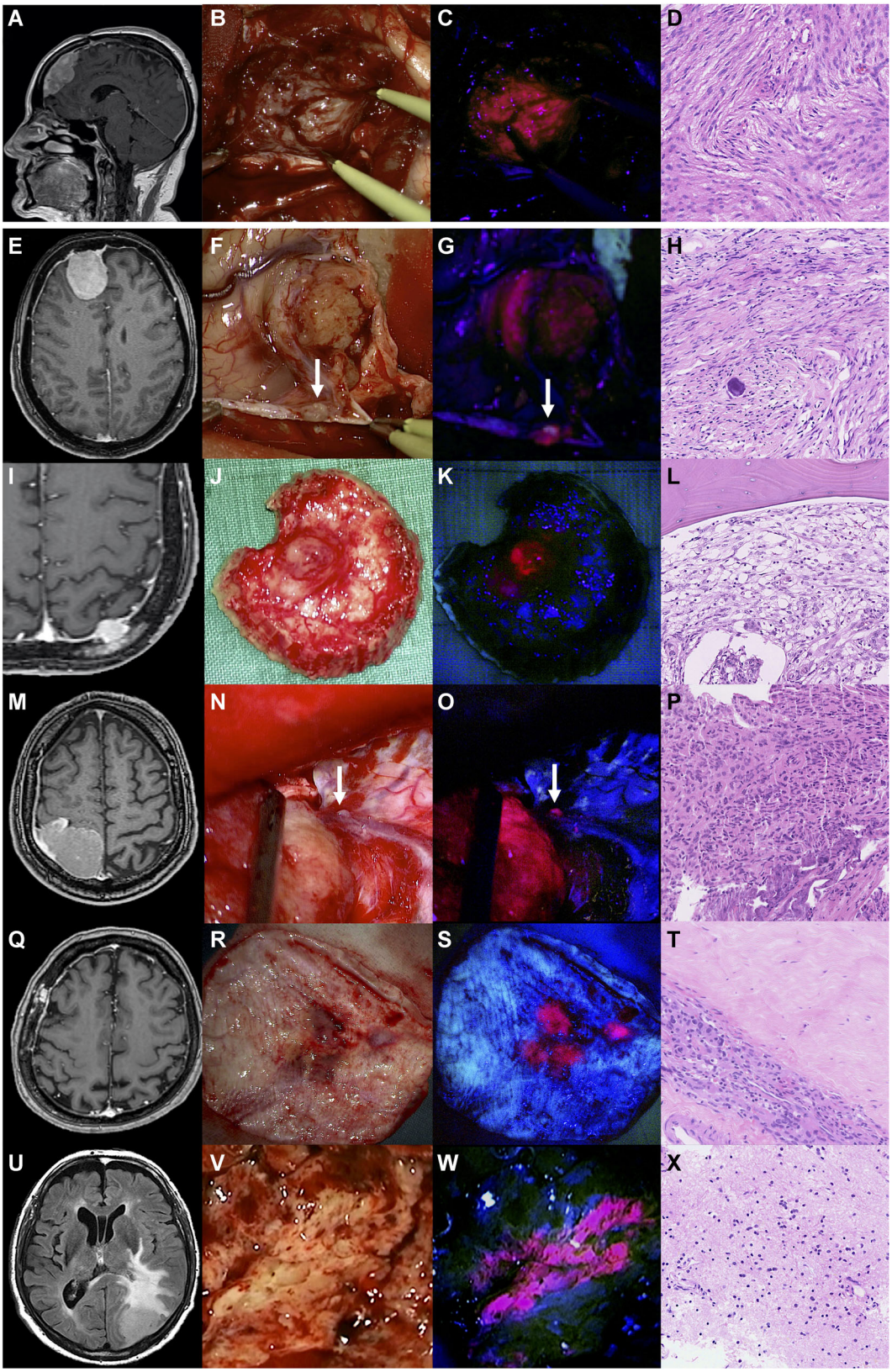

Figure 1 Continued.

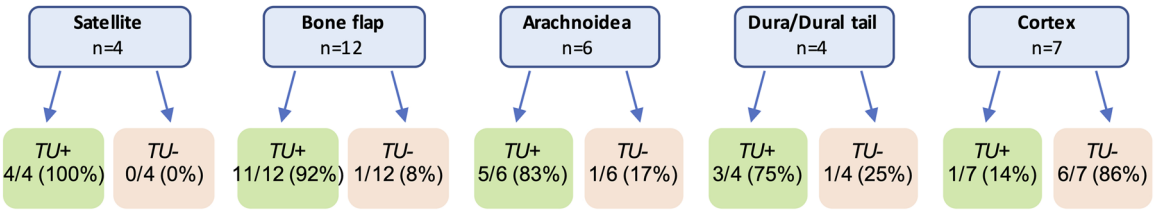

Fig. 2. Different sites of peritumoral tissue and the corresponding histopathology in surgery of intracranial meningiomas after preoperative 5-ALA administration. In the majority of fluorescing samples from satellite lesions (100%), bone flaps (92%), arachnoidea (83%), and dura/dural tail (75%) tumor tissue was present according to the histopathological analysis. In contrast, tumor cells were detected in only 14% of samples derived from fluorescing cortex. 5-ALA, 5-aminolevulinic acid.

(73%) of 33 cases. In contrast, in nine (27%) of 33 fluorescing samples no tumor cells were detected despite visible fluorescence. Therefore, the PPV of visible fluorescence to identify tumor cells in the group of samples from peritumoral tissue was 73%. It is of note that fluorescing samples with lack of tumor tissue were found only in a subgroup of samples from peritumoral tissue. In detail, tumor tissue was present in fluorescing samples in all four (100%) satellite lesions as well as the majority of samples collected from suspected bone flap infiltration (11 of 12 samples; 92%), arachnoidea (five of six samples: 83%), and the dura/dural tail (three of four samples; 75%). In contrast, tumor cells were absent in the majority of fluorescing samples from the adjacent cortex (six of seven samples; 86%). Interestingly, six (86%) of these seven fluorescing samples were collected from high-grade meningiomas (4 WHO grade III and 2 WHO grade II meningiomas). Despite the absence of tumor cells in six (86%) of seven fluorescing samples from the adjacent cortex, distinct reactive tissue alterations were found in the histopathological work-up in all six tumor-free samples. Additionally, vascular proliferation was observed in two fluorescing cortex samples with lack of tumor cells. See also Figures 1 and 2.

All tissue samples including samples from tumor bulk and peritumoral tissue. The PPV of visible fluorescence for visualizing meningioma cells in our entire study cohort of tumor bulk and peritumoral tissue was 95.3%. We found a significantly higher diagnostic accuracy of visible fluorescence for detecting meningioma tissue derived from the tumor bulk as compared to samples from peritumoral tissue (100% vs. 73%; $P < 0.001$).

Fig. 1. Examples of surgically treated meningiomas after 5-ALA administration with detailed analysis of specific regions of the tumor bulk or peritumoral tissue: preoperative MRI, conventional white-light surgery, fluorescence status, and corresponding histopathology. (**A**–**D**) Tumor bulk: Preoperative T1-weighted MRI demonstrates a frontal convexity meningioma (**A**). The tumor is removed under white-light surgery (**B**) and shows visible 5-ALA fluorescence (**C**). Histopathological analysis of a sample with visible fluorescence from the tumor bulk confirms the presence of meningioma tissue (**D**). (**E**–**H**) Satellite lesion: Preoperative T1-weighted MRI reveals a frontal convexity meningioma (**E**). A small satellite lesion distant to the meningioma bulk not visible on MRI and hardly recognizable under conventional white-light microscopy (**F**) can be clearly detected by visible fluorescence (**G**; white arrow). The corresponding sample of the fluorescing satellite lesion demonstrates distinct meningioma tissue (**H**). (**I**–**L**): Bone flap: Preoperative T1-weighted MRI shows a parietal convexity meningioma with suspected bone flap involvement (**I**). The removed bone flap demonstrates a suspicious bone infiltration in the center (**J**). Violet-blue excitation light is able to clearly visualize the bone involvement by visible fluorescence (**K**). The corresponding tissue sample from fluorescing bone confirms the presence of meningioma tissue. (**M**–**P**): Arachnoidea: Preoperative T1-weighted MRI shows a parietal convexity meningioma (**M**). Infiltration of the arachnoidea is hardly recognizable under conventional white-light microscopy (**N**), but can be clearly identified with assistance of visible fluorescence (**O**; white arrow). The corresponding fluorescing sample of arachnoidea reveals distinct meningioma tissue (**P**). (**Q**–**T**): Dura: T1-weighted MR images demonstrate a frontal intraosseous meningioma (**Q**). After resection of a frontal intraosseous meningioma, the underlying dura shows only slight abnormalities (**R**), but violet-blue excitation light is able to identify several fluorescing spots on the dura (**S**). The corresponding fluorescing sample from these spots shows meningioma tissue with infiltrative growth into the dura (**T**). (**U**–**X**): Adjacent cortex: Preoperative T1-weighted MRI reveals an occipital convexity meningioma with a large peritumoral edema (**U**). During resection of the meningioma, the performing neurosurgeon has the impression of an infiltrative growth under white-light microscopy (**V**) and the adjacent cortex demonstrates unequivocal fluorescence (**W**). The corresponding tissue sample from fluorescing cortex shows absence of tumor cells, but reveals reactive tissue alterations. The tumor was finally classified as a WHO grade III meningioma. 5-ALA, 5-aminolevulinic acid; MRI, magnetic resonance imaging.

TABLE 3. Literature Overview on Studies With Separate Biopsies and the Corresponding Histology in Intracranial Meningiomas

	Samples with 5-ALA+ biopsies	WHO grade	Fluorescing tissue samples with tumor cells in histology from different locations					
			Tumor bulk	Bone flap, infiltrated bone	Dura/ dural tail	Arachnoidea	Satellite lesions	Adjacent cortex
Kajimoto et al. [21]	6	I, II	–	–	5/6 (83%)	–	–	–
Della Puppa et al. [24]	57	I, II	–	57/57 (100%) "infiltrated bone, bone flap"	–	–	–	–
Valdes et al. [20]	20	I	20/20 (100%)	–	–	–	–	–
Cornelius et al. [22]	8	I, II, III	–	–	–	–	–	8/8 (100%) "tumor-brain interface"
Millesi et al. [14]	7	I, II, III	–	7/7 (100%) "bone flap"	–	–	–	–
Knipps et al. [25]	42	I, II	41/42 (98%)	–	–	–	–	–
Scheichel et al. [27]	7	I, II	–	7/7 (100%) "infiltrated bone"	–	–	–	–
Present study	191	I, II, III	158/158 (100%)	11/12 (92%)	3/4 (75%)	5/6 (83%)	4/4 (100%)	1/7 (14%)

5-ALA+, 5-aminolevulinic acid positive, WHO, World Health Organization.

DISCUSSION

Intraoperative visualization of tumor tissue in meningioma surgery is challenging for the neurosurgeon, especially in case of tumor infiltration of peritumoral tissue such as the bone flap, dura/dural tail, arachnoidea, adjacent cortex, or satellite lesions. Therefore, residual tumor tissue might remain undetected during meningioma surgery and result in local tumor recurrence. Recently, 5-ALA fluorescence was also described as a promising marker for intraoperative visualization of intracranial meningiomas apart from the main indication of HGG [14,16,20]. In this sense, Kajimoto et al. [21] published the first series of 24 meningioma patients in 2007 and observed visible 5-ALA fluorescence during surgery in 83% of cases. Subsequent studies were able to confirm these first observations and reported the presence of visible 5-ALA fluorescence during meningioma surgery in 77–96% of cases [14–16,20,22,23]. In the largest series to date including altogether 204 meningiomas, we observed intraoperative 5-ALA fluorescence in 91% of cases [14]. Interestingly, we found in this study that 5-ALA fluorescence was useful to identify also peritumoral tissue, in particular, infiltrated bone flaps and satellite lesions during meningioma surgery [14]. Nevertheless, the histopathological correlate of visible 5-ALA fluorescence in intracranial meningiomas is still unclear. In this sense, previous studies (see Table 3) are limited by the small number of patients, inclusion of meningiomas with specific WHO grades only, primary focus on certain localizations such as infiltrated bone and on quantitative measurements of 5-ALA induced protoporphyrin IX (PpIX) accumulation [20,24,25]. However, the histopathological analysis of tumor bulk as well as peritumoral tissue in a large series would be of major importance to improve the precision of meningioma surgery and therefore reduce the risk of local tumor recurrence.

Present Study

On the basis of these current limitations of the literature, we thus performed a retrospective study on 85 meningiomas of all WHO grades to investigate the PPV of visible 5-ALA fluorescence. For this purpose, 191 fluorescing samples from the tumor bulk as well as peritumoral tissue were included and histopathologically analyzed in this study.

Tumor bulk tissue and histopathology. According to histopathological assessment, meningioma tissue was present in our study in all 158 fluorescing samples from the tumor bulk leading to a PPV of 100%. This is in accordance with the study conducted by Valdes et al. [20] reporting presence of meningioma tissue in all 20 separate biopsies with visible 5-ALA fluorescence of the tumor bulk in a cohort including only WHO grade I meningiomas. Furthermore, Knipps et al. [25] analyzed 42 fluorescing biopsies of the tumor bulk in a series consisting of WHO grade I and II meningiomas. Similar to our observations, the authors found meningioma tissue in the vast majority of fluorescing biopsies derived from the tumor bulk

(41 of 42 samples; 98%) [25]. In sum, our current data in the largest cohort of separate tissue samples with visible 5-ALA fluorescence from the tumor bulk including all WHO grades demonstrate a very high PPV for detecting meningioma tissue and confirm the preliminary observations of the first smaller studies [20,25]. Therefore, 5-ALA fluorescence represents a powerful technique to support the neurosurgeon in visualizing tumor tissue within the tumor bulk to achieve the surgical goal of a complete meningioma removal.

Peritumoral tissue and histopathology. The analysis of fluorescing samples from peritumoral tissue confirmed meningioma tissue in 73% of 33 cases in our study leading to a PPV of 73%. Thus, the PPV of visible fluorescence for detecting meningioma tissue was significantly lower in samples from peritumoral tissue as compared to tumor bulk tissue. Most likely, this finding can be explained by differences in the presence of tumor tissue based on the specific localizations of the collected peritumoral tissue samples.

Bone flap: Bone tissue is frequently affected by intracranial meningiomas and represents an important site for tumor recurrence [26]. In our study, meningioma tissue was present in the vast majority of fluorescing samples (11 of 12 samples; 92%) from suspicious bone flaps. A previous study by Della Puppa et al. [24] investigated fluorescing samples from suspected bone infiltration in a series of WHO grade I and II meningiomas. In accordance to our findings, the authors confirmed meningioma tissue by histopathology in all 57 fluorescing samples with suspected bone infiltration [24]. This is in line with two further studies by Millesi et al. [14] and Scheichel et al. [27] confirming the presence of tumor tissue in all seven analyzed fluorescing bone samples. Due to the very high frequency of tumor tissue in meningiomas with fluorescing bone flaps, 5-ALA fluorescence is useful to visualize the precise extent of tumor infiltration within this area. This will facilitate in future the intraoperative decision-making to either perform a tailored removal of infiltrated bone flap tissue with assistance of visible 5-ALA fluorescence or replace the infiltrated bone flap by a cranioplasty if a large portion of the bone is affected.

Dura/dural tail: The precise morphological correlate of the dural tail is controversially discussed and corresponds most likely to tumor infiltration or venous congestion [28–31]. As the dural tail as well as tumor infiltrated dura are sites for potential recurrence, these regions are generally included in the surgical plan of meningioma resection. In our study, we found presence of tumor tissue in 75% of four cases with fluorescing dura/dural tail. Similarly, Kajimoto et al. [21] confirmed presence of tumor tissue in five (83%) of six fluorescing dural tail cases. According to the previous study by Millesi et al. including altogether 204 meningiomas, visible fluorescence was not present in any of the 89 investigated dural tails and thus visible fluorescence within the dura/dural tail is a rare event. Nevertheless, in these rare cases of visible fluorescence within the dura/dural tail, the presence of tumor tissue has to be suspected and thus we recommend removing areas of visible fluorescence in these regions whenever possible to reduce the risk of local tumor recurrence.

Satellite lesions: Small satellite lesions might occur in the proximity to the main meningioma bulk and constitute the potential origin of tumor recurrence [32,33]. Unfortunately, such satellite lesions are usually hardly recognizable during conventional tumor resection under white-light microscopy. According to histopathological analysis, tumor tissue was found in all four fluorescing satellite lesions in our study. To our knowledge, this is the first report analyzing the histopathological correlate of fluorescing satellite lesions distant to the meningioma bulk. Consequently, we suggest investigating regions in proximity to the meningioma bulk for potential satellite lesions with assistance of 5-ALA fluorescence.

Arachnoidea: Meningiomas arise from cap cells in the arachnoidea, and thus this region represents an important site for potential residual tumor tissue in the course of resection [34]. In our study, tumor tissue was present in 83% of six fluorescing samples from the arachnoidea. To our knowledge, our study provides the first data on the histopathological correlate of fluorescing arachnoidea. Thus, 5-ALA fluorescence is also beneficial to visualize tumor infiltrated arachnoidea and thus we suggest removing areas of visible fluorescence in these areas whenever possible to reduce the risk of local recurrence.

Adjacent cortex: Finally, brain invasion represents an important factor for tumor recurrence in intracranial meningiomas [35]. Therefore, brain invasion was added as a diagnostic criterion for atypia in meningiomas in the updated WHO classification released in 2016 [19]. However, visualization of such brain invasion during surgery of meningiomas is a major challenge for the neurosurgeon. Nevertheless, tumor infiltration was observed in only one (14%) of seven fluorescing samples from the adjacent cortex in our study. According to our data, 5-ALA fluorescence is not useful to visualize brain infiltration during meningioma surgery and thus we do not recommend removing this frequently false positive fluorescence within the cortex. In contrast to our study, Cornelius et al. [22] confirmed tumor infiltration in all eight samples of the "tumor-brain interface" with visible 5-ALA fluorescence. Despite the absence of tumor cells in most fluorescing cortex samples in our study, we found distinct reactive tissue alterations in all tumor-free samples and additionally vascular proliferation in selected cases. Interestingly, the vast majority of samples from the fluorescing cortex in our study were derived from high-grade meningiomas (WHO grade II and III). Thus, the significance of 5-ALA fluorescence in the adjacent cortex of meningiomas has to be analyzed in future studies.

Study Limitations

(i) First of all, this represents a retrospective study with its known shortcomings. (ii) Furthermore, our study

cohort was characterized by an imbalance in tissue samples from the tumor bulk ($n = 158$) and peritumoral tissue ($n = 33$). Thus, the sample size of each subgroup (bone, cortex, arachnoid, dura, and satellite lesions) of peritumoral tissue samples was quite small and calculation of PPV or diagnostic value of 5-ALA for detecting tumor tissue at the margins of a meningioma resection cavity was not reasonable. The preliminary data of our study will be the basis to design future prospective studies with the ability to collect a sufficient number of samples from the different subgroups including bone, cortex, arachnoid, dura, and satellite lesions aside from samples from the tumor core. This approach will allow to perform the abovementioned subgroup analyses (PPV, diagnostic value of 5-ALA for detection of tumor tissue at the margin). (iii) Furthermore, residual tumor tissue might occur also in other sites such as large sinuses or the optic canal during meningioma surgery other than the regions analyzed in this retrospective study. Therefore, future studies should also investigate further important sites for meningioma recurrence. (iv) Finally, the intraoperative assessment of visible fluorescence is observer-dependent and thus low amounts of fluorescence might not be recognized during meningioma surgery by every neurosurgeon. To objectify fluorescence detection, spectroscopic probes are nowadays available that are capable of quantitatively measuring the intratumoral 5-ALA induced PpIX concentrations during neurosurgical procedures [13,36,37]. Thus, 5-ALA induced PpIX concentrations of the tumor bulk as well as peritumoral tissue should be correlated in addition to visible fluorescence with histopathology in future studies with a large sample size.

CONCLUSIONS

In this largest study to date, we analyzed the PPV of visible 5-ALA fluorescence in tissue samples derived from surgery of intracranial meningiomas. According to histopathological analysis, meningioma tissue was present in all samples with visible fluorescence of the tumor bulk as well as most fluorescing specimens of peritumoral tissue such as satellite lesions, bone flaps, arachnoidea, and dura/dural tail. Consequently, 5-ALA fluorescence supports the neurosurgeon in detecting residual tumor tissue at the relevant surgical sites to optimize meningioma surgery and minimize the risk of local tumor recurrence. The significance of the frequently false positive fluorescence of the adjacent cortex of meningiomas has to be clarified in future studies.

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