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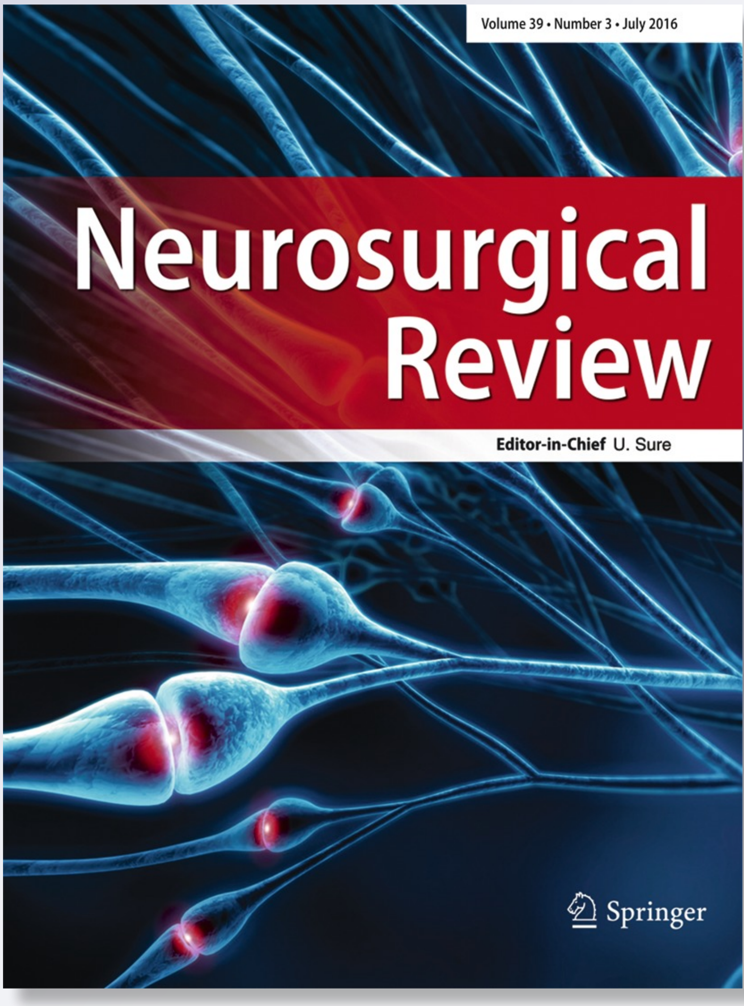

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ORIGINAL ARTICLE

Laser biospectroscopy and 5-ALA fluorescence navigation as a helpful tool in the meningioma resection

A. A. Potapov [1] · S. A. Goryaynov [1] · V. A. Okhlopkov [1] · L. V. Shishkina [1] · V. B. Loschenov [2] · T. A. Savelieva [2] · D. A. Golbin [1] · A. P. Chumakova [3] · M. F. Goldberg [4] · M. D. Varyukhina [5] · A. Spallone [6,7]

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Abstract 5-aminolevulinic acid (5-ALA) is a natural precursor of protoporphyrin IX (PP IX), which possesses fluorescent properties and is more intensively accumulated in tumor cells than in normal tissue. Therefore, the use of 5-ALA in the surgical treatment of intracranial tumors, particularly gliomas, has gained popularity in the last years, whereas its use in other intracranial pathological entities including meningiomas has been reported occasionally. This study describes a series of 28 patients with intracranial meningiomas, who were administered 5-ALA for a better visualization of tumor boundaries. Twelve patients underwent also laser spectroscopic analysis in order to confirm the visual impression of tumor tissue visualization. Bone infiltration was readily demonstrated. In one case, the tumor recurrence could have been prevented by removal of a tumor remnant, which would possibly have been better recognized if spectroscopic analysis had been used. Fluorescent navigation (FN) is a useful method for maximizing the radicality of meningioma surgery, particularly if the tumor infiltrates the bone, the skull base, and/or the surrounding structures.

Keywords Fluorescent navigation · 5-ALA · Laser spectroscopic analysis · Intracranial meningioma · Surgical treatment

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Introduction

The use of fluorescent diagnostics in brain tumor surgery was initially documented by Moore et al. in 1948 [1] in the premodern neuroimaging era. The effect of fluorescein accumulation in brain tumors, likely associated with blood-brain barrier damage, helped obtaining more defined information about tumor localization. However, fluorescein had a marked local and general toxicity, caused allergic reactions, and had a prolonged elimination time. Therefore, its routine use was not recommended generally. However, in spite of the failure of the fluorescein staining method, investigations on tumor coloring techniques continued [2].

The development of photodynamic technology in neurooncology took another peak of interest with the introduction of a new photosensitizer, 5-aminolevulinic acid (5-ALA), a natural precursor of protoporphyrin IX (PpIX), which possesses fluorescent properties. PpIX was found to be more intensively accumulated in tumor cells than in normal tissues. Several reasons are suggested to be responsible for this phenomenon [3–5], such as tissue's decreased permeability to 5-ALA; selective capturing of 5-ALA by tumor cells; changes in the activity of plasma enzymes, which are involved in hem synthesis; and reduction of the ferrochelatase activity (the enzyme which catalyzes the transformation of Pp IX to the hem).

A multicenter project, which was pursued in Germany by 17 centers, was the first prominent clinical study in the field of fluorescence navigation (FN) in brain tumor surgery. The research demonstrated high rates of radical resection of glial tumors (from 35 to 65 %) and increased six-month survival in patients in whom this method had been used [6]. At the same time, no statistically significant effect on the overall survival rate was identified. Nevertheless, this technology has attracted an increased attention of neurosurgeons resulting in more reports on FN, as well as the application of this method for other central nervous system tumors [4, 7–16] including intracranial meningiomas [16–20]. However, the assessment of FN's sensitivity and specificity was not demonstrated clearly and in particular, no comparison was made between the data obtained from visible fluorescence, and the data obtained from laser biospectroscopy in meningiomas of different World Health Organization (WHO) grades. The goal of our study was to evaluate the advantages of the intraoperative FN in the surgery of intracranial meningiomas, as well as to compare the quantitative analysis of visible fluorescence and the laser biospectroscopy data in a series of patients with such tumors operated in our institute.

Material and methods

Twenty-eight patients with intracranial meningiomas who underwent fluorescent navigated surgery in the Burdenko Neurosurgery Institute in 2011 and 2012 were included in the analysis. The first 21 had already been briefly reported in a previous publication [9]. The series consisted of six males and 22 females aged 29 to 74 years, with a mean age 58 years. All but five patients underwent primary meningioma resection. The following distribution of tumor location was observed: convexity—8, parasagittal—12, tentorial—6, basal—2. Histologically, 24 had grade 1 meningiomas, and four had grade 2 meningiomas, according to the WHO classification. Table 1 summarizes the main data of the present case material.

After obtaining an informed consent and information concerning normal functioning of the liver and kidneys, the patients received two to three hours before surgery a solution of hydrochloride of 5-aminolevulinic acid (Alasens®, SSC "NIOPIK" Russian Federation) a dose 20 mg/kg 5-ALA. The study on the 5-ALA-mediated neurosurgery had been approved by the ethical committee of the Burdenko Neurosurgery Institute since 2007.

A Carl Zeiss Pentero microscope with a fluorescent module was used in 23 surgeries. Five surgeries were performed with a Carl Zeiss NC4 microscope and a Karl Storz endoscope, equipped with filters for fluorescence detection. The intensity of visible fluorescence was assessed by visual observation using the following scale: 0—no fluorescence, 1—poor rose-colored fluorescence, 2—bright red fluorescence, and 3—very intensive scarlet fluorescence. Six surgeons conducted the procedure of assessment, and a minimum of three surgeons were present during each surgery. In addition, a laser spectroscopy was also utilized in the 12 more recent cases in order to more accurately measure PpIX accumulation.

After the removal of the tumor mass, the operating microscope is switched to a "blue 400" mode, and the tumor bed, its matrix, remnants of the capsule when present, adjacent brain tissue, bone structures, and adventitia of adjacent vessels, are carefully inspected for possible further tumor resection.

Biospectranalysis was performed using a LESA-01 (BIOSPEC JSC®, Russian Federation) spectrum analyzer (Fig. 1). This has a fiber optic probe which consists of one central (for delivery) and six surrounding (for collecting) metal-coated quartz fibers with the core diameter of 200 μm. The fiber spacing is 250 μm (center-to-center) with total diameter of the probe tip of 1.8 mm. The delivery fiber is coupled with a He-Ne laser (632.8 nm) with 10-mW output power, measured at the probe tip. The collecting fibers are connected to a spectrometer with a "cut-off" filter inserted at the entry for suppressing the laser scattered light. One part of the laser light is scattered back from the tissues into the collecting fibers, while the other part is absorbed by the endogenous chromophores and ALA-induced protoporphyrin IX, and then reemitted as the fluorescence with the other wavelength. The insertion of an appropriate "cut-off" filter into the spectrometer entry allowed to detect both fluorescence and backscattering light components at the same time.

The fluorescence index (FI) was calculated in relative units (r.u.) as the ratio of the fluorescence intensity of PP IX at 690–730 nm to the intensity of backscattered laser radiation. Protoporphyrin IX (Pp IX) content measurements were made during surgery in parallel with multiple biopsy analysis. The Simpson classification was used to assess the degree of surgical radicality [21], and the World Health Organization (WHO) classification was used to identify histological types of tumors.

Statistical analysis was conducted using the Pearson's correlation coefficient. Statistical significance was indicated when p value was lower than 0.05 ($p > 0.05$).

Results

Neither death nor significant complications occurred during hospital stay of the patients. Moreover, we have not detected complications associated with the administration of 5-aminolevulinic acid. Tumor fluorescence was observed in all cases except one (96.4 %).

Figures 2, 3, and 4 show a typical example of convexity meningioma (WHO grade I) with bright fluorescence and high levels of PpIX accumulation during spectral analysis. A decrease in the fluorescence intensity was observed in a fibrous portion of meningiomas (Fig. 5) and during surgeries

Table 1 Main clinical and radiological information on the present patients

No	Localisation	Sex, age	Primary/ recurrent	Preoperative steroids	Histology	Grade	Fluorescence	Maximal spectrum of the tumor	Simpson grade	Invasion of the bone flap	Karnofsky score before/ after surgery
1	Convexital	F, 52	P	Yes	Meningotheliomatous	I	2	19.3	1	No	90/90
2	Tentorial	F, 58	P	No	Atypical	II	1	38.33	2	No	90/90
3	Tentorial	F, 74	P	Yes	Mixed	I	1	31.36	4	No	90/90
4	Parasagittal	F, 74	P	No	Mixed	I	3	27.06	2	No	90/90
5	Convexital	F, 67	P	Yes	Psammomatous	I	2	15.52	2	No	80/80
6	Parasagittal	F, 46	P	No	Mixed	I	3	53.67	2	No	70/70
7	Basal	F, 62	P	Yes	Meningotheliomatous with psammoma bodies	I	2		2	No	90/90
8	Convexital	F, 59	P	Yes	Atypical	II	0	46	1	Yes	80/80
9	Multiple Convexital and Basal	M, 47	R	Yes	Atypical	II	1	53.04	4	No	60/60
10	Parasagittal	M, 64	P	Yes	Psammomatous	I	1	9.39	2	Yes	90/80
11	Parasagittal	F, 71	P	Yes	Fibroplastic	I	1		4	No	70/70
12	Tentorial	M, 46	P	Yes	Fibroplastic	I	1		4	No	80/90
13	Parasagittal	M, 42	P	No	Fibroplastic	I	2	45.11	1	Yes	70/80
14	Convexital	F, 66	P	No	Psammomatous	I	3		1	Yes	90/90
15	Tentorial	F, 51	P	Yes	Fibroplastic	I	1		2	No	90/90
16	Parasagittal	F, 29	P	No	Mixed	I	2	30.95	1	No	70/70
17	Parasagittal	F, 50	R	Yes	Meningioma with nuclear polymorphism	I	1		1	No	70/80
18	Tentorial	M, 51	P	Yes	Mixed	I	1		2	No	80/80
19	Basal	F, 74	P	No	Mixed	I	3		1	No	80/90
20	Parasagittal	F, 50	P	No	Mixed	I	1		2	No	90/90
21	Parasagittal	F, 51	R	No	Atypical	I	1		1	Yes	90/90
22	Convexital	F, 66	P	No	Psammomatous	I	1	47.63	1	Yes	90/90
23	Parasagittal	F, 58	P	No	Mixed	I	3		2	No	70/70
24	Convexital	F, 59	P	Yes	Mixed	I	3		1	No	70/80
25	Convexital	F, 74	P	Yes	Psammomatous	I	1		1	Yes	80/80
26	Parasagittal	M, 73	R	No	Atypical	II	2	33.92	1	Yes	90/90
27	Parasagittal	F, 48	R	Yes	Fibroplastic	I	3	25.53	2	No	90/90
28	Tentorial	F, 32	P	Yes	Mixed	I	1	121.93	2	No	70/70

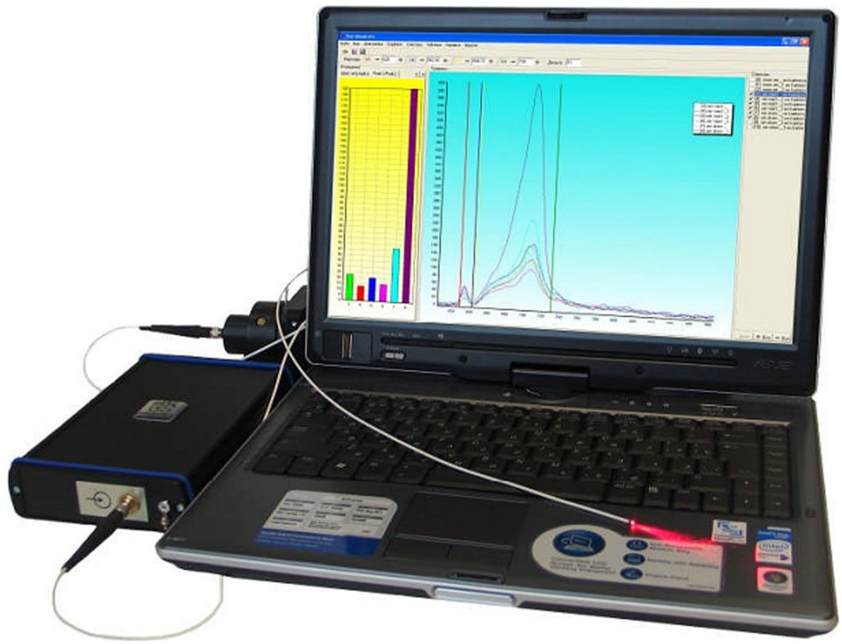


Fig. 1 1 LESA-01-BIOSPEC

complicated by severe bleeding. In five cases, bleeding occurred from parasagittal veins, venous lacunas, or tumor vessels in the process of resection. The fluorescence intensity was very low in all these situations. We have encountered a complete absence of visible fluorescence in only one case, a 59-year-old female with highly vascularized convexity meningioma of the occipital region (WHO grade I), which bled severely during the surgery. At the same time, spectral analysis of the tumor ex vivo revealed a significantly increased signal level.

Tumor location and previous surgeries did not appear to affect the degree of PpIX accumulation. We also found no correlation between the level of anaplasia and the observed fluorescence intensity or intensity of the PpIX accumulation spectra.

In twelve cases, the fluorescent spectra were measured in several tumor portions. A linear correlation was found between the level of visually perceived video fluorescence and the FI determined spectroscopically (Table 2). Tumor spectral characteristics varied in a broad range from 9.39 to 121.93 r. u. (average 32.64 r. u.), but increased values of the spectra were observed in all cases (Fig. 6). Out of 12 patients in whom spectroscopy was utilized, four spectra volume had been increased in order to detect tumor remnants, which were not visible at lower spectra volume range. These figures, although not insignificant, are too small to allow any statistically based

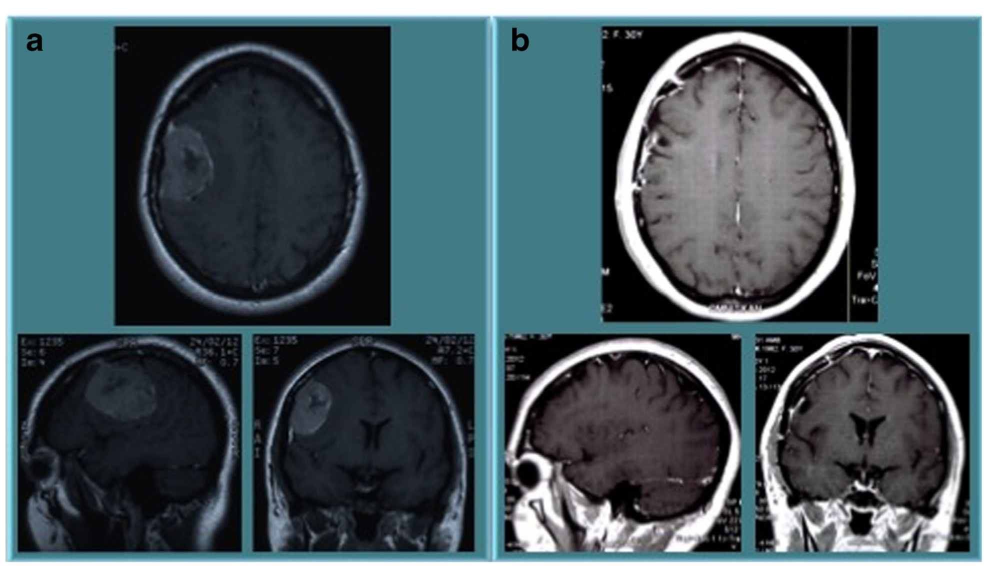


Fig. 2 Preoperative and postoperative MRI of case 17 (mixed meningioma)

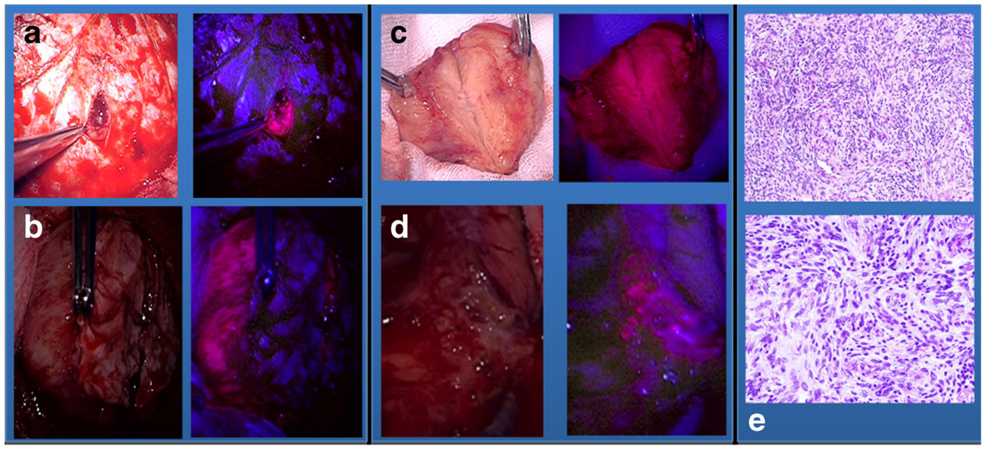


Fig. 3 Fluorescence of mixed meningioma during resection (intraoperative pictures). **a**, **b** Opening the dura and exposure of the underlying tumor. **c** The resected meningioma. **d** A residual of the tumor in the resection bed. **e** The tumor biopsy revealed a mixed meningioma (hematoxylin and eosin). **a**–**d** Left—control in the white light mode; right—control in the fluorescence mode

conclusion about spectroscopic fluorescence sensitivity for small volume tumor remnants.

Adding spectroscopy to the fluorescence navigation allowed in the present case material detecting, among others, two small residual parasagittal meningiomas, several cases of infiltrated tumor-adjacent hyperostotic bone, and one case of sphenoid wing meningioma which infiltrated the adventitia of a M2 branch. In total in ten out the 24 present cases, the surgical strategy was changed according to the result of fluorescing navigation. Five were recurrent and/or bone infiltrating convexity meningiomas, three were skull base tumors, two, above mentioned ones, were parasagittal meningiomas. One of these patients had a multiple, basal and convexity, locations.

Radical resection (Simpson I–II) was achieved in 24 patients. In other cases, patients underwent subtotal resections owing to the tumor invasion of major vascular structures. However, in all cases, visualization of fluorescence helped achieve more careful dissection of small tumor fragments in order to minimize the chances of recurrence (Figs. 7 and 8). In particular, a conspicuous fluorescence staining of the invasion of the bone flap was easily identified during surgery in eight cases. Consequently, the affected bone was resected in seven cases, and the site of the invasion was thoroughly drilled in order to remove all neoplastic cells in one patient (Fig. 9).

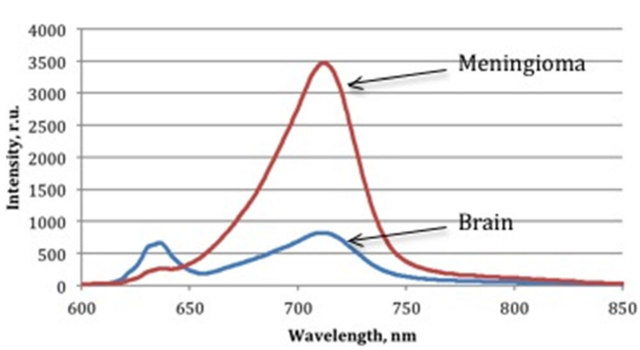


Fig. 4 Case 17. Laser biospectroscopy profiles of normal brain tissue and meningioma measured in the course of the surgery

Hyperostosis as well as tumor borders are quite well visible under microscopic light. However, fluorescence navigation increases the accurateness of tumor visualization also because the 5-ALA staining remains quite well visible for a few hours after its injection; thus, it can be definitely useful in defining the dural “tail” infiltration and the tumor-invaded hyperostotic bone.

Systematic follow-up was possible only in 15 patients (our institute receives patients from all ex Soviet Union countries, and many patients are thus difficult to follow up). Two cases of recurrence were observed at an average follow-up of eleven months. One of these cases harbored a multiple convexity and skull base tumor, which had been taken to subtotal resection in one session, and exhibited a little tumor regrowth of the skull base lesion at the six-month routine MRI control.

The other case was a parasagittal grade II meningioma, which had apparently been removed totally, and showed a small relapse at the six-month MRI control. Spectroscopic analysis was not applied in this case, but, as we suppose, if this method had been used, the likely remnant of the lesion could have been detected and removed, and the recurrence would thus have been prevented. Interestingly, a suspicious staining was visually observed in the adjacent, potentially functional cortex, but this was not considered a sufficient reason for widening the surgical resection because of a potential risk of functional impairment.

No statistical correlation was detected between tumor grade and either video fluorescence intensity either fluorescence index as determined spectroscopically.

Discussion

5-ALA-assisted intraoperative navigation is a useful method for fluorescent diagnostics in patients with high-grade gliomas [6, 9, 13–15, 22]. The use of 5-ALA-induced PpIX fluorescence has shown promises as a surgical adjunct for maximizing the extent of surgical resection in gliomas. However, using

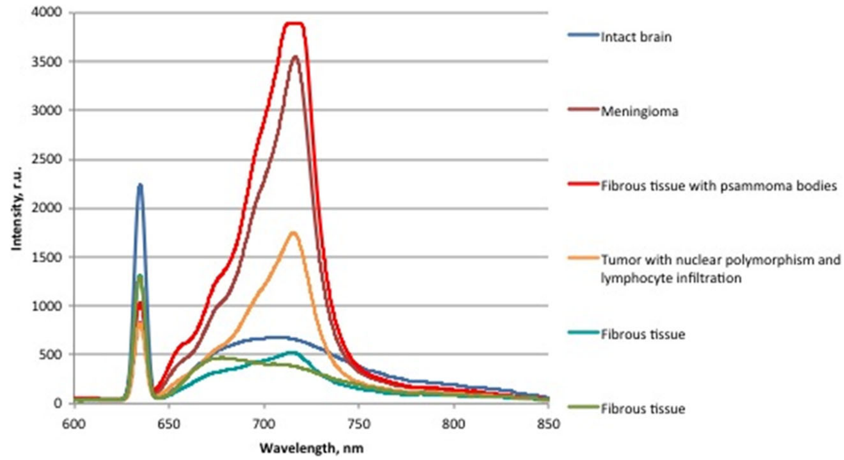


Fig. 5 Case 5. Laser biospectroscopy profiles of biopsies obtained from different sites of the operative wound

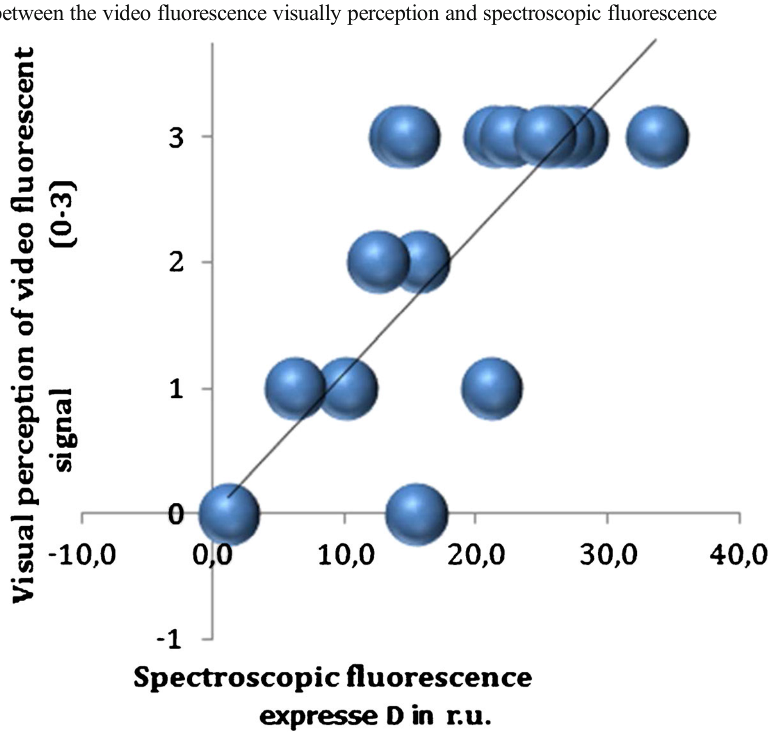
5-ALA in meningioma surgery has been studied only occasionally. Apart from the present research, which was also partly described in a previous publication [22], the most prominent series of meningioma operated on using FN were published by Collucia et al. (33 patients) [18] and Kajimoto et al. (27 patients) [19]. Both studies reported on convexity, parasagittal, and basal meningiomas of different malignancy degrees. We found no descriptions of the laser spectroscopy method in these publications.

The recurrence rate of meningioma depends on various factors: the tumor grade, completeness of resection, postoperative radiation therapy, etc. [7, 23, 24]. In this perspective, the main weapon of a neurosurgeon might be the achievement of maximum tumor resection.

The degree of surgical radicality may be decreased by a number of conditions: (1) the tumor infiltrates the surrounding structures including the dura mater, the bone, and the adjacent brain tissue since the infiltration area, and intact tissue are difficult to differentiate; (2) major vessels and sinuses, folds of the dura, and the cortex sulci may conceal small fragments of the tumor; and (3) secondary nodes of the tumor are sometimes located separately from the main tumor mass [19, 25–28, 29]. FN is feasible as a technique that can help overcome these difficulties.

Our observations, as well as publications of other authors [18, 19], indicate that FN allows to obtain additional information about the infiltrative tumor growth and bone invasion. Therefore, this method may be very useful for surgery in

Table 2 Linear correlation between the video fluorescence visually perception and spectroscopic fluorescence



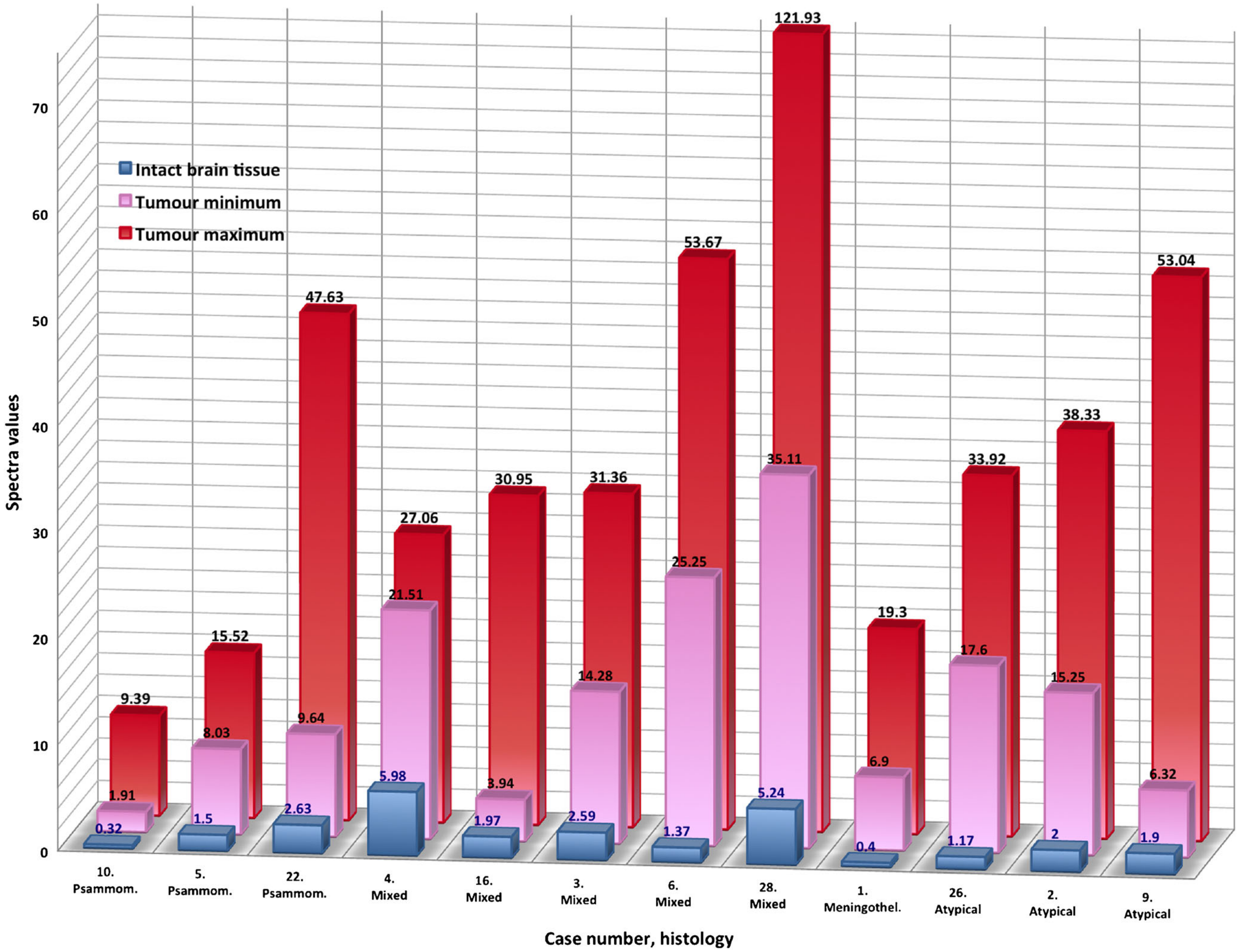


Fig. 6 Intraoperative quantitative 5-ALA accumulation in 12 cases. Note the different levels of PP IX in different types of meningiomas

recurrence meningioma [19], skull base meningiomas [8], and spinal meningiomas [11].

Pp IX has a marked absorption peak (Soret band) in violet areas of visible spectra which are commonly used to induce the fluorescence. However, this violet light is absorbed not only by Pp IX but also by many other types of biomolecules that results in low penetration depth of violet light into biological tissue. The other disadvantage of violet light for Pp IX fluorescence excitation is the spectral dependence of tissue absorption on the wavelength which obliges to calculate optical properties of the tissue in the whole spectral range to consider the absorption of both excitation and fluorescence light.

At the same time, a Q-band of Pp IX absorption spectra, which is not so intense as a Soret band, is found in the biological transparency window (where absorption of light is much lower than in violet spectral region). Therefore, the red laser light penetrates deeper into tissues, and the detected spectrum does not need absorption corrections to analyze fluorescence. As a result, our method, unlike the method proposed by Valdes et al. (30), does not require to calculate optical properties for the quantitative determination of Pp IX concentration considering absorption of both excitation and fluorescence light. Furthermore, our method allows simultaneous recording of both fluorescence and diffuse reflectance spectra that reduces the period of time used to register full spectral information from a single area and increases accuracy. Thus, the use of red light for inducing Pp IX fluorescence is the main advantage of our method in comparison with the method which uses other lights of shorter wavelengths for fluorescence excitation.

Fluorescence may offer no advantages in the surgical removal of convexity meningiomas; however, it could be useful in checking the completeness of infiltrated dura resection in some suspicious cases. The case of parasagittal-falx-meningiomas seems to be quite different: in two out of the ten present cases, spectroscopic PP IX enhancement revealed tumor residual after an apparently total microsurgical removal of the mass.

Fluorescence navigation may be undoubtedly valuable in recurrent and/or deep-seated meningioma, in which checking

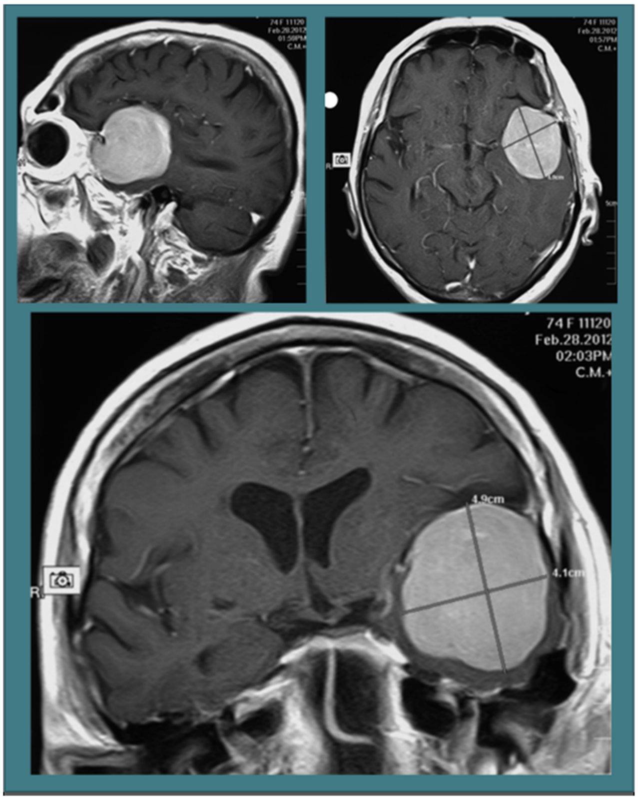


Fig. 7 Case 20. Preoperative MRI with contrast enhancement

the completeness of the resection of the infiltrated dura is as a rule very difficult.

The use of the red light to excite the fluorescence of PP IX allows the light to penetrate the tissue deeper, than the violet light, which is traditionally used in video fluorescence systems. This effect is related to the fact that the red light, unlike violet light, is within the biological transparency window that is the portion of spectrum of light. Spectranalysis of red light fluorescence, unlike other lights, does not require sophisticated methods.

In the present case material, we observed that spectral characteristics of different tumor portions may vary in a broad range. However, a highly significant ($p < 0.01$) correlation existed between visual perception of video fluorescence and the spectroscopic fluorescence index. This means that in general visual impression at surgery could give a reasonably good idea of the fluorescence 5-ALA capture in meningiomas cases, although individual cases may represent exceptions. In two cases, in which spectroscopy bleeding had been significant, video signal gave results quite different from those of the spectroscopic method, a fact which would appear to give strength to the objective spectroscopic measurement of 5-ALA fluorescence emission that we used. This would play an important role in the detection of tumor burden in difficult meningioma cases, in whom the interface tumor-non timorous tissue is unclear and video FN does not give the necessary evidence.

In our series, the light mode fluorescence was obscured by blood in one case. However, due to a deeper penetration of the red excitatory laser in spectroscopy, a high level of protoporphyrin IX accumulation was observed, and the tumor was better identified and completely removed. This observation suggests that the use of laser spectroscopy offers indubitable benefits in conditions of an impeded visible fluorescence such as intraoperative bleeding [30]. In fact, in meningiomas with infiltrative characteristics, it can be particularly difficult to

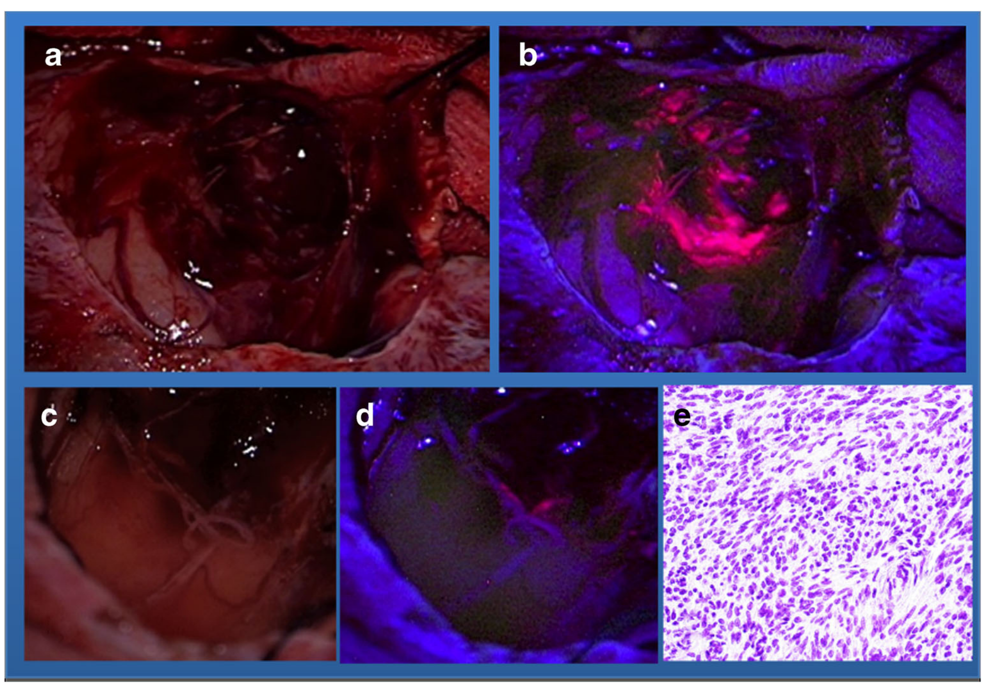


Fig. 8 Case 20. **a**, **b** Intraoperative fluorescence of meningioma in the course of resection. **c**, **d** Fluorescence of vessel's adventitia separated from the tumor. **e** The tumor biopsy revealed a mixed meningioma (hematoxylin and eosin). **a**, **c** Control in the white light mode; **b**, **d** control in the fluorescence mode

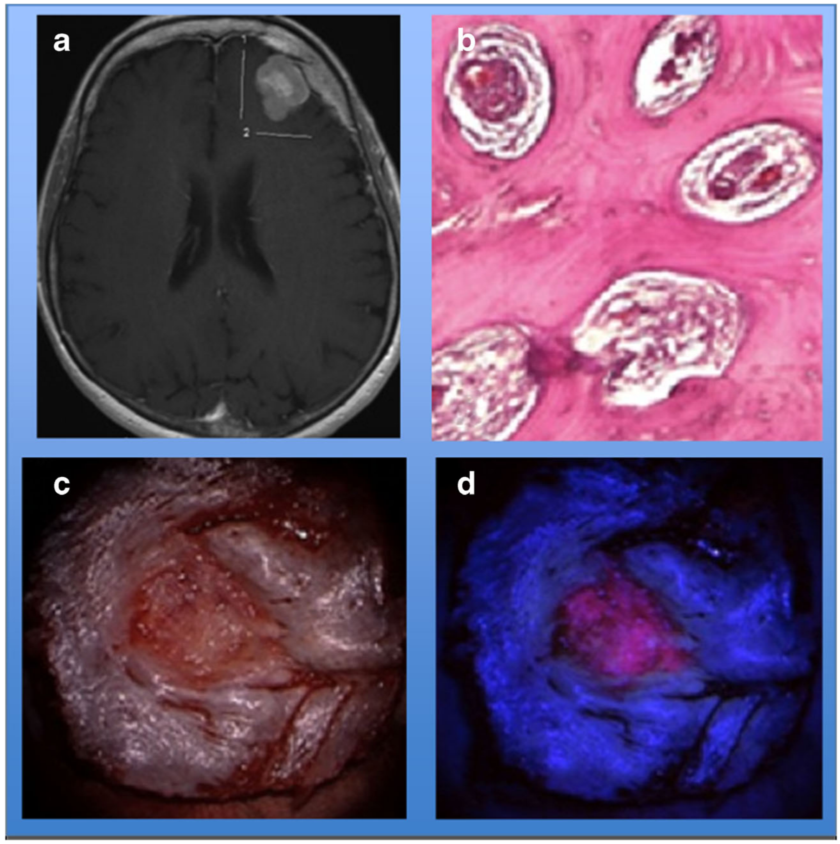


Fig. 9 Case 15. Invasion of the bone flap. **a** Preoperative MRI. **b** Histology of the affected bone flap. Haversian channels are filled with tumor cells (hematoxylin and eosin). **c** Control in the white light mode. **d** Control in the fluorescence mode. Bright fluorescence of the affected bone

distinguish traumatized surrounding brain tissue from tumor remnants even if FN is used, as it occurred in one patient mentioned above. Thus, the present data on the use of laser spectroscopy, as an adjunct to FN, are undoubtedly encouraging. Also, further investigations are required to clarify possible correlations between histological and spectral characteristics of meningioma since no conclusions can be drawn on this point in accordance with the present data.

In conclusion, 5-ALA-assisted intraoperative navigation has a potential use in the surgery of intracranial meningiomas,

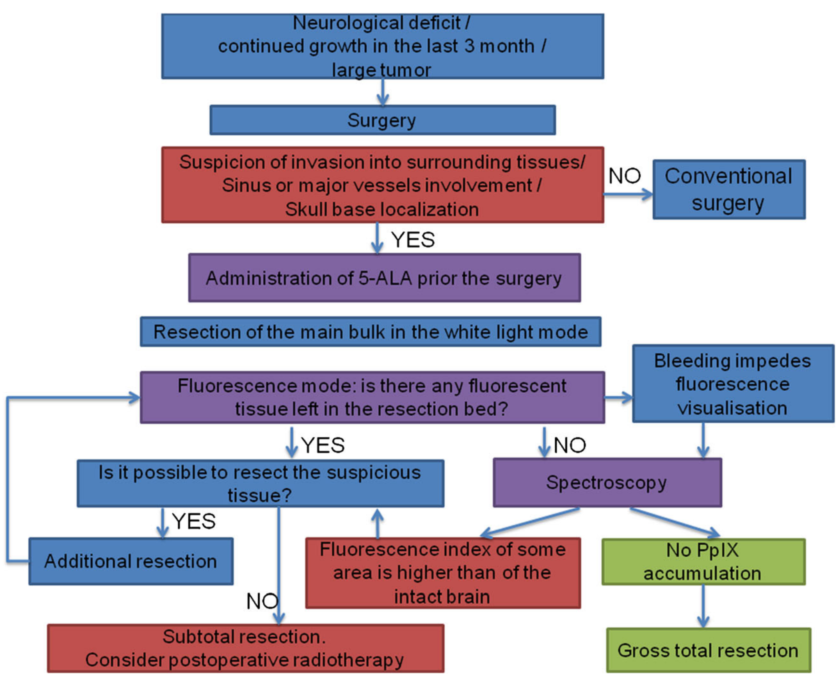


Fig. 10 Algorithm of FD and laser spectroscopy in meningioma surgery

specifically in cases of recurrence, in tumors located at the base of the skull and in those which infiltrate vascular structures and/or the overlying bone. A possible paradigm of the FN application in meningioma surgery is shown in Fig. 10. The cost of 5-ALA is likely to have been the main reason for preventing its widespread use due to understandable economical considerations, particularly in the setting of the global economic crisis. Maybe, if the cost reduction in the whole market would be possible, some reservations concerning 5-ALA application would be overcome, and its use, potentially beneficial in the surgery of intracranial tumors of different histologic types, as suggested also by the present study, would be widely, if not eventually routinely, recommended. Further investigations are needed to assess the impact of the application of FN and laser spectroscopy on the recurrence rate of intracranial meningiomas, as our experience seems to suggest.

5-ALA, 5-aminolevulinic acid; FN, fluorescent navigation; PP IX, protoporphyrin IX; MRI, magnetic resonance imaging; WHO, World Health Organization.

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Compliance ethical standards

Conflict of interest The authors declare that they have no competing interests.

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