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Role of neurochemical navigation with 5-aminolevulinic acid during intraoperative MRI-guided resection of intracranial malignant gliomas

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ABSTRACT

Objective: To evaluate the role of the neurochemical navigation with 5-aminolevulinic acid (5-ALA) during intraoperative MRI (iMRI)-guided resection of the intracranial malignant gliomas.
Methods: The analysis included 99 consecutive surgical cases. Resection of the bulk of the neoplasm was mainly guided by the updated neuronavigation based on the low-field-strength (0.3 T) iMRI, whereas at the periphery of the lesion neurochemical navigation with 5-ALA was additionally used.
Results: In total, 286 tissue specimens were obtained during surgeries for histopathological examination. According to iMRI 98 samples with strong (91 cases), weak (6 cases), or absent (1 case) fluorescence corresponded to the bulk of the lesion and all of those ones contained tumor. Out of 188 tissue specimens obtained from the "peritumoral brain," the neoplastic elements were identified in 89%, 81% and 29% of samples with, respectively, strong (107 cases), weak (47 cases) and absent (34 cases) fluorescence. Positive predictive values of the tissue fluorescence for presence of neoplasm within and outside of its boundaries on iMRI were 100% and 86%, respectively.
Conclusion: Neurochemical navigation with 5-ALA is useful adjunct during iMRI-guided resection of intracranial malignant gliomas, which allows identification of the tumor extension beyond its radiological borders.

1. Introduction

Although according to strict criteria of evidence-based medicine, there is still insufficient prove that aggressive image-guided surgery of intracranial gliomas positively influences prognosis [1,2], multiple studies demonstrated significant association between resection rate and overall, progression-free, malignant transformation-free, neurological deterioration-free, and seizure-free survival [3–12]. Additionally, gross total tumor removal augments effectiveness of the adjuvant therapies [6,13]. Nowadays, the rate of radiologically total removal of the cerebral gliomas in selected groups of patients varies widely from 45% to 97% [4–7,9,10,12,14–23], and in our own experience constitutes 46% [24–27]. Use of intraoperative MRI (iMRI) seemingly has the strongest impact on such aggressive surgical practice [7,9,12,20,24–29]. Among other methods neurochemical navigation based on 5-aminolevulinic acid (5-ALA)-induced tissue fluorescence demonstrated particularly promising results and showed high effectiveness for intraoperative identification of the tumor borders [4,10,12,14,15,19,21–23,29–39]. In Tokyo Women's Medical University application of both techniques for guidance of brain tumor surgery was initiated more than decade ago [24–28,31,40,41]. The objective of the present study was evaluation of the role of the neurochemical navigation with 5-ALA during iMRI-guided resection of the intracranial malignant gliomas. Additionally, safety of 5-ALA administration was assessed.

2. Methods and materials

From May 2004 to June 2010, 97 consecutive patients with malignant gliomas underwent iMRI-guided tumor resection with

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additional neurochemical navigation using 5-ALA in the Intelligent Operating Theater of the Tokyo Women's Medical University. Two patients underwent such surgery twice at the time of initial diagnosis and at recurrence, which for the purpose of the data analysis were considered as separate cases.

2.1. General data

There were 64 men and 35 women. Their age varied from 17 to 83 years (median, 53 years). There were 80 newly diagnosed and 19 recurrent gliomas. Contrast enhancement of the tumor on T_1-weighted MRI was noted in 87 cases.

Tumor resection was performed using standard microneurosurgical technique according to the previously described concept of the information-guided surgery (Fig. 1) [25–27]. Removal of the bulk of the lesion was guided by the updated neuronavigation based on the low-field-strength (0.3 T) iMRI (AIRIS II^{TM}; Hitachi Medical Corporation, Tokyo, Japan). At the periphery of the tumor its removal was additionally guided by neurochemical navigation with 5-ALA and histopathological monitoring of the resected tissue [25–27,42].

2.2. Neurochemical navigation with 5-ALA

Clinical use of 5-ALA for neurochemical navigation during removal of the intracranial gliomas was approved by the Ethics Committee of the Tokyo Women's Medical University. Within 2 to 4 h before induction of anesthesia for craniotomy and tumor removal the patients were given perorally a single dose (20 mg/kg) of 5-ALA (Cosmo Bio Co., Ltd.; Tokyo, Japan) as a freshly prepared 50 mL of water solution. For observation of the tissue fluorescence and neurochemical navigation during resection of the neoplasm D-light (Karl Storz Co., Ltd., Tuttlingen, Germany) was used. The light source of the excited wave (375 to 440 nm) was applied to evoke a red fluorescence (635 nm) that was visible for the naked eye after passing through a low cut filter (Kenko Y2: cut under 480 nm; Kenko Tokina Co., Ltd., Tokyo, Japan). Additionally, a blue laser diode of a quartz laser source (VLD-Mi; M&M Co., Ltd., Tokyo, Japan) with a wavelength of approximately 405 nm was used for detection of the protoporphyrin IX fluorescence in the resected pathological tissue. Intensity of tissue fluorescence was assessed subjectively by 2 attending neurosurgeons (YM, TM) and graded as strong, weak, and absent (Fig. 2).

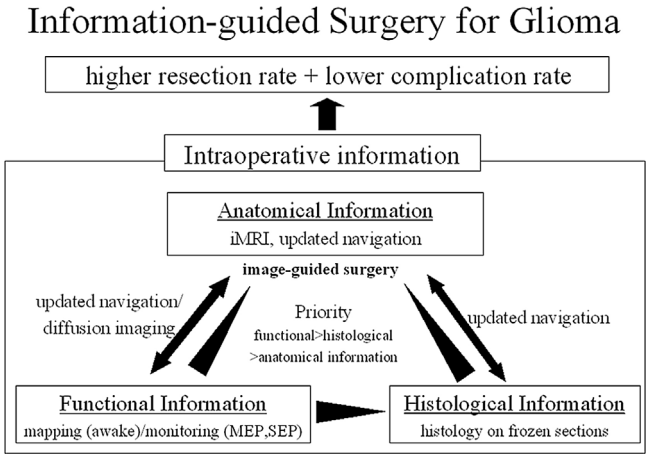

Fig. 1. Main principles of the information-guided surgery for glioma. To maximize resection rate and minimize the risk of postoperative neurological morbidity anatomical data obtained with intraoperative MRI (iMRI) are integrated with functional and histological information. MEP, motor evoked potentials; SEP, somatosensory evoked potentials. From Muragaki et al. [26].

Safety of 5-ALA administration was assessed according to the Common Terminology Criteria for Adverse Events version 3.0 [43]. Eyes and skin of patients were protected from the strong light sources during 24 h after administration of the drug [14,29,30,37].

2.3. Histopathological investigation

In total, during resection of 99 tumors, 286 separate biopsy specimens were obtained (mean number per case, 3 ± 2; median, 2; range, 1–10). Final histopathological diagnosis of the tumor was established according to the current WHO criteria [44] on the paraffin-embedded tissue sections stained with hematoxylin and eosin and appropriate antibodies for immunohistochemistry.

2.4. Postoperative evaluation of the tumor resection rate

Evaluation of the tumor resection rate was done by comparison of the preoperative and postoperative MRI obtained within 3 days after surgery, using 1.5 T clinical scanner (ExcellArt; Toshiba Medical Systems, Tokyo, Japan). In contrast-enhanced tumors (87 cases) any contrast-enhanced area on postoperative T_1-weighted images, beside evident vessels, was considered as residual neoplasm. In non-enhancing gliomas (12 cases) any hyperintense area on T_2-weighted images was considered as residual neoplasm.

2.5. Statistics

Chi-square test was used for statistical comparisons of the groups. The level of significance was determined at $P < 0.05$.

3. Results

Mean tumor resection rate was $95\% \pm 8\%$ (range, 60–100%). In 51 cases (52%) no residual tumor was identified on postoperative MRI. There was no perioperative mortality. Early complications were noted in 66 patients (67%) and are characterized in Table 1. At 3 months after surgery the neurological status of 9 patients (9%) still was worse than before intervention. Histopathological investigation revealed 32 WHO grade III gliomas and 67 WHO grade IV gliomas (Table 2).

During surgery 5-ALA-induced tissue fluorescence was revealed in all 99 cases and its maximum intensity was characterized as strong (93 cases; 94%) or weak (6 cases; 6%). In total, 251 tissue samples from the fluorescent areas were obtained for histopathological examination and tumor was identified in 230 cases (92%). Neoplastic elements were revealed in 186 out of 198 (94%) and in 44 out of 53 (83%) specimens obtained from the areas of strong and weak fluorescence, respectively ($P = 0.0108$).

Table 1
Early postoperative complications in the present series.

Complications	Number of cases
Motor deficit	24 (24%)
Seizures	12 (12%)
Aphasia	11 (11%)
Disturbances of consciousness	7 (7%)
Dysarthria	5 (5%)
Deep venous thrombosis	5 (5%)
Fever	5 (5%)
Visual disturbances	4 (4%)
Sensory deficit	2 (2%)
Hemianopsia	2 (2%)
Impairment of hearing	2 (2%)
Dysphagia	2 (2%)

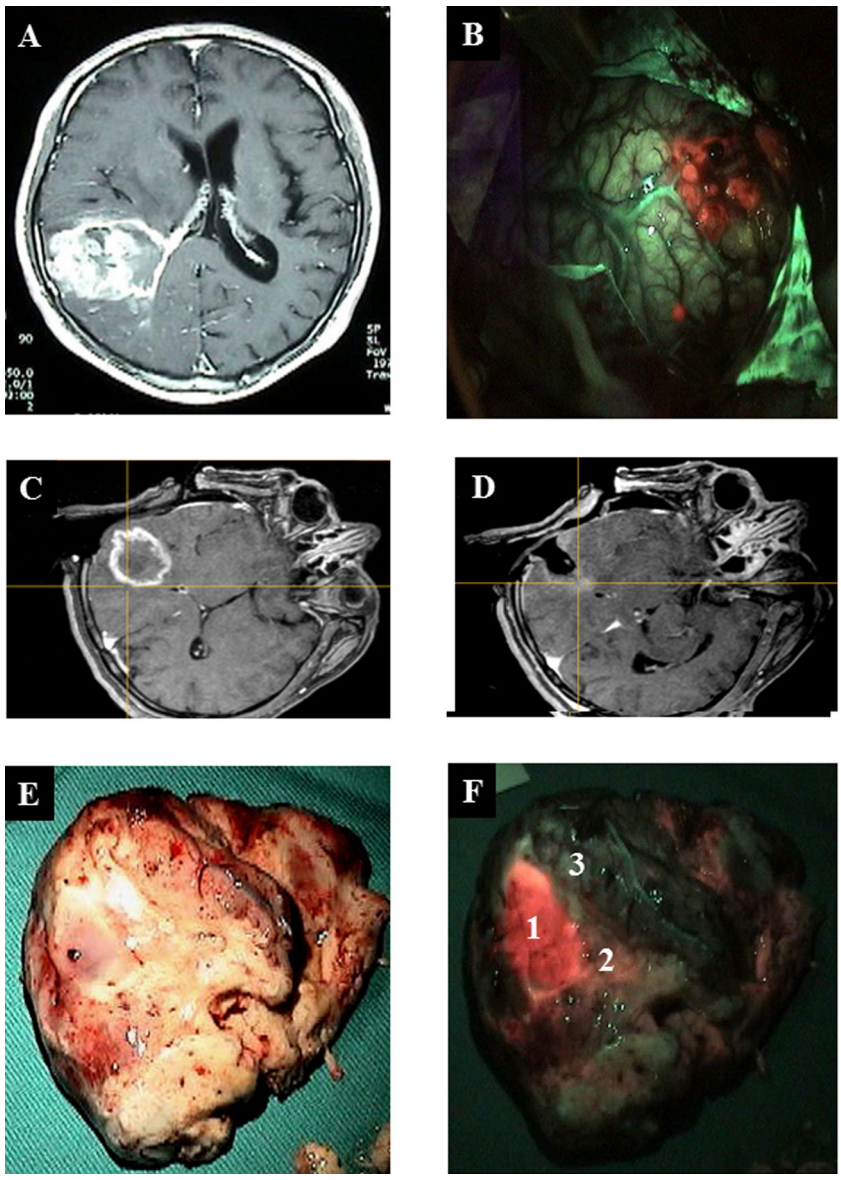

Fig. 2. Evaluation of 5-ALA-induced tissue fluorescence during surgical resection of the right parietal high-grade glioma: preoperative MRI demonstrating heterogeneous contrast-enhancing tumor (A), identification of the fluorescence on the surface of the neoplasm before its resection (B), neuronavigation based on post-contrast T_1-weighted images obtained with low-field-strength intraoperative MRI before (C) and after (D) tumor resection, the bulk of the mass removed *en block* (E), and additional identification of the fluorescence of the pathological tissue (F). Different intensity of the tissue fluorescence was graded as strong (1), weak (2), and absent (3).

Table 2
Histopathological types of malignant gliomas in the present series.

Histopathological type of the tumor	Number of cases
Anaplastic astrocytoma (WHO grade III)	8 (8%)
Anaplastic oligoastrocytoma (WHO grade III)	10 (10%)
Anaplastic oligodendroglioma (WHO grade III)	11 (11%)
Other non-specified WHO grade III gliomas	3 (3%)
Glioblastoma (WHO grade IV)	63 (64%)
Other non-specified WHO grade IV gliomas	4 (4%)
Total number	99 (100%)

According to contrast-enhanced iMRI 97 tissue samples from the fluorescent areas (strong intensity, 91 cases; weak intensity, 6 cases) corresponded to the bulk of the tumor. In all these specimens histopathological evaluation revealed presence of the neoplasm. Other 154 tissue samples from the areas of fluorescence (strong intensity, 107 cases; weak intensity, 47 cases) were obtained from the "peritumoral brain." In 133 of these specimens (86%) histopathological examination revealed neoplastic elements, which presented in 95 out of 107 (89%) and in 38 out of 47 (81%) specimens obtained from the areas of strong and weak fluorescence, respectively ($P = 0.1868$).

Other 35 tissue samples obtained during surgery for histopathological examination corresponded to the areas with absent fluorescence. According to contrast-enhanced iMRI only one such specimen corresponded to the bulk of the neoplasm and it contained neoplastic elements. In 10 out of 34 tissue samples (29%) obtained from the areas with absent fluorescence located in the "peritumoral brain" histopathological investigation disclosed presence of tumor.

In overall, 5-ALA-induced tissue fluorescence had 92% positive predictive value (PPV) for presence of glioma in the histopathological specimen (Table 3).

Table 3
Diagnostic efficacy of the identified 5-ALA-induced tissue fluorescence for histopathological identification of the tumor presence in the specimen.

Diagnostic parameters	Overall (%)	Tumor bulk* (%)	Peritumoral brain* (%)
Sensitivity	95 (93–97)	99 (94–100)	93 (90–96)
Specificity	53 (42–62)	NA***	53 (43–62)
Positive predictive value	92 (90–93)	100 (95–100)	86 (83–89)
Negative predictive value	69 (55–80)	0 (0–95)	71 (56–82)
Diagnostic accuracy**	89 (85–92)	99 (94–100)	84 (78–88)

Borders of 95% confidence intervals are shown in parentheses. NA, non-applicable.
* According to low-magnetic-field intraoperative MRI.
** Relative combined number of true positive and true negative cases.
*** No false positive and true negative results were noted.

3.1. Diagnostic efficacy of iMRI and neurochemical navigation with 5-ALA for identification of the tumor presence

In all tissue specimens ($N = 98$), which according to contrast-enhanced iMRI were obtained from the bulk of the tumor and corresponded to strong (91 cases), weak (6 cases), or absent (1 case) fluorescence, histopathological investigation revealed neoplastic elements. Therefore, in such cases tissue sampling based on the anatomical information alone had 100% PPV for tumor presence.

In all tissue specimens ($N = 188$), which according to contrast-enhanced iMRI were obtained from the "peritumoral brain," histopathological investigation revealed neoplastic elements in 143 cases (76%). Diagnostic accuracy of 5-ALA-induced tissue fluorescence for tumor presence in the histopathological specimen did not differ significantly between newly diagnosed and recurrent malignant gliomas ($P = 0.8181$), WHO grade III and IV tumors ($P = 0.4179$), newly diagnosed WHO grade III and IV tumors ($P = 0.4593$), and recurrent WHO grade III and IV tumors ($P = 0.7339$).

3.2. Safety of 5-ALA administration

There were no serious adverse events or significant abnormalities in hepatic function associated with peroral administration of 5-ALA. In 3 cases (3%) mild nausea and vomiting were noted, whereas one patient experienced mild photosensitivity reaction.

4. Discussion

Neurochemical navigation with 5-ALA during resection of gliomas is based on the effect of its accumulation in the neoplastic cells and areas with impaired blood-brain barrier (BBB) and further conversion into protoporphyrin IX, which fluorescence becoming visible under illumination with 375–440 nm ultraviolet light [11,29,37]. The effect is preserved during 12 h after administration of the drug, whereas its peak is marked in 6–8 h with tumor/normal brain fluorescence ratios ranging from 6:1 to 10:1 [29,30]. It was demonstrated that presence of 5-ALA-induced tissue fluorescence and its intensity well correspond to the areas of contrast enhancement on MRI [17,31,34] and radioisotope uptake on PET [36,38], histopathological identification of the tumor in the tissue sample [14–16,30–32,34,36,38,39,45], and greater aggressiveness of the neoplasm [16,30,34].

Fluorescence-guided surgery results in increased resection of malignant gliomas [4,10,12,14,15,23,36,46]. In a large prospective multicenter randomized phase III trial Stummer et al. [4] showed that compared to conventional microsurgery use of neurochemical navigation with 5-ALA leads to significantly greater proportion of radiologically complete resections of glioblastomas (65% vs. 36%; $P < 0.0001$), smaller volume of the residual tumor (medians 0 cm^3 vs. 0.7 cm^3; $P < 0.0001$), and better progression-free survival at 6 months after intervention (41% vs. 21%: $P = 0.0003$). Recently such beneficial results were corroborated by the retrospective VISIONA study, which evaluated habitual neurosurgical practice in Spain [23]: assessment of 251 eligible cases from 18 clinics demonstrated greater proportions of complete resections of malignant gliomas with the use of 5-ALA (67% vs. 45%; $P = 0.000$) and progression-free survivors at 6 months after removal of glioblastoma (69% vs. 48%; $P = 0.002$). It should be noted that peroral administration of 5-ALA in a dose 20 mg/kg is sufficiently safe [4,10,14,22,29,31–33,37,39], which was also confirmed in the present study.

Nevertheless, the erroneous results of the neurochemical navigation with 5-ALA are not uncommon. Absence of the tissue fluorescence is typical for low-grade gliomas due to relative preservation of the BBB [17,30,36,45] and intrinsic mechanisms for fast elimination of the drug [37]. Beside it may be caused by specific features of the tumor metabolism characterized by overexpression of cadherin 13 gene [47], or by administration of steroids and bevacizumab [17,37]. 5-ALA-induced fluorescence depends on mitochondrial content and cellular density, and usually absent in the areas of necrosis and scar tissue [14,16,30,32,34,36,45,48]. Fluorescence may be not detected due to suboptimal position of the light source (too distant from the area of interest or with slanted angle of illumination) [18,29,37], intervening layer of normal tissue covering the tumor [14,17,18,29,34,37,39], or presence of blood on the tissue surface [30,45]. During prolonged surgeries possible problems with detection of fluorescence may result from its time-dependent deterioration or bleaching due to excessive or prolonged use of the ultraviolet light or microscope illumination [29,30]. Finally, tissue fluorescence may be below the threshold of the visual perception [34,35]. On the other hand, false positive tissue fluorescence may be identified in the areas of high vascularization, reactive astrocytosis and fibrosis, macrophages infiltration, inflammation, brain edema, or BBB impairment in the absence of the neoplastic elements [31,36,37,45,48,49]. In the series of Utsuki et al. [49] such finding was noted in 4% of newly-diagnosed and 45% of recurrent malignant gliomas. Specific cerebral structures, such as choroid plexus, ependyma and pia mater, may demonstrate wide, albeit mild, fluorescence [15,16,32,37]. If attempts to detect 5-ALA-induced fluorescence are performed without dimming of the lightening in the operating room, the normal brain may falsely appear red [14,37]. In overall, in the pooled cohort of 780 cases extracted from 13 published studies tissue fluorescence had 91% sensitivity, 59% specificity, 85% PPV, and 71% NPV for histopathological identification of malignant glioma [36], which seems comparable to our results presented herein.

There is limited number of reports on combined use of iMRI and 5-ALA during glioma resection. In the recent retrospective study Roder et al. [12] did not find any advantages in addition of the neurochemical navigation to iMRI-guided resection of glioblastomas. Moreover, according to their results iMRI is superior to 5-ALA with regard to residual tumor volume and total resection rate, particularly in lesions located in or in close vicinity to eloquent brain structures. Their series included 19 patients in whom both techniques were applied during surgery, but analysis of their effectiveness was limited to removal of the contrast-enhanced part of the tumor. Moreover, it may be assumed that use of fluorescence guidance was mainly done during initial resection phase, which is completely opposite to our strategy presented herein. Contrary, Eyupoglu et al. [18] prospectively applied dual intraoperative visualization approach in 37 cases of presumably malignant gliomas. Combined use of both techniques was especially effective in tumors adjacent to eloquent brain areas (Sawaya functional grade II [3]) and increased the extent of resection in this subgroup from 71.7% to 100%. In the series of Tsugu et al. [17] 19 patients underwent surgery with the use of both iMRI and 5-ALA. The former was more effective for removal of tumors,

which did not demonstrate tissue fluorescence, providing 20.8% gain of resection rate in comparison to 0.8% in 5-ALA-positive cases. The authors concluded that combination of the intraoperative imaging and fluorescence guidance has a synergistic effect on attainment of the more precise and radical glioma resections [17,18].

In our practice we use low-magnetic-field (0.3 T) iMR scanner, which, however, provides high-quality images due to several technological advances, particularly integration of the RF receiver coil with Sugita head-holder (Head-holder coil; Mizuho Ltd., Tokyo, Japan) [24–28]. The device demonstrated high sensitivity for detection of the residual glioma, which was confirmed by postoperative MRI investigations, and in no one case of the present series unexpected residual tumor was disclosed. Meanwhile, our results showed important complimentary role of iMRI and 5-ALA during resection of malignant gliomas. According to presented data the removal of the bulk of the mass may be effectively guided by neuroimaging alone, since it provided 100% PPV for tumor presence in the resected pathological material. In the same time evaluation of the 5-ALA-induced tissue fluorescence beyond radiological margins of the neoplasm may be extremely helpful, since it permits to attain more aggressive tumor resection. According to Schucht et al. [46] complete elimination of the fluorescent tissue yielded a 6 mm mean additional rim (range, 0–10 mm) of resection margin beyond the border of contrast enhancement on T_1-weighted MRI. Such aggressive surgery may have positive impact on patient's survival [14,21].

There were some concerns that 5-ALA-induced fluorescence may be reduced in recurrent malignancies due to effects of the previous radiotherapy and chemotherapy [37]. Our series included 19 patients with recurrent malignant gliomas, but in these cases the diagnostic accuracy of tissue fluorescence for tumor detection beyond its radiological border did not differ significantly compared to newly diagnosed neoplasms. Nabavi et al. [32] in prospective Phase II study of 5-ALA-guided resection of recurrent malignant gliomas revealed 93% PPV of tissue fluorescence for tumor detection in normal-appearing brain. Therefore, it seems that prior irradiation and chemotherapy does not preclude effective use of neurochemical navigation for resection of recurrent gliomas.

It is evident, that complete resection of glioma represents highly desirable, but not the ultimate goal of surgery, and should be always balanced against the risk of postoperative neurological morbidity. Of note, 5-ALA-induced tissue fluorescence may extend up to 1 cm beyond the radiological border of the contrast-enhancing tumor [46] reflecting its intermingling with functioning brain structures [10,14,16,32]. In fact, in the present series the rate of early postoperative complications (67%) was nearly two-times greater than in our usual practice with the use of iMRI alone for surgery of gliomas [24,25], while at 3 months thereafter just 9% of patients did worse than before intervention. Significant risk of neurological deterioration during initial postoperative period after aggressive resection of the fluorescent-positive tissue was frequently noted before [4,10,15,16,21–23,32,39], and patients with recurrent gliomas and/or preoperative neurological deficit, especially non-responsive for steroids administration, are particularly susceptible for functional impairment after removal of the neoplasm [10,22].

5. Conclusion

Evaluation of 5-ALA-induced tissue fluorescence may be considered as useful adjunct during iMRI-guided resection of intracranial malignant gliomas, which allows identification of the tumor extension beyond its radiologically identified boundaries. It may be rather helpful for intraoperative decision-making on the optimal lesion resection and for more objective evaluation of the completeness of mass removal.

Conflicts of interest

From April 2010 till March 2014, Mr. Shinobu Yamada was enrolled in the Doctorate Program of the Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University. He is full-time employer of the Nobelpharma Co., Ltd., which distributes 5-aminolevulinic acid in Japan for application during photodynamic diagnosis and therapy.

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