Neuroendoscopic Cylinder Surgery and 5-Aminolevulinic Acid Photodynamic Diagnosis of Deep-Seated Intracranial Lesions

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■ BACKGROUND: **Microscopic detection of intracranial brain tumors with 5-aminolevulinic acid (5-ALA) has proven extremely useful, and reports the use of 5-ALA have recently increased. However, few reports have described 5-ALA photodynamic diagnosis (PDD) using a neuroendoscope. We performed neuroendoscopic 5-ALA PDD for various brain lesions and present a procedure using only a neuroendoscope.**

■ METHODS: **We describe the diagnosis of 20 intracranial brain lesion cases with a 5-ALA–guided fluorescence endoscope. A light-emitting diode that emitted either white light or 400- to 410-nm violet light was attached to a neuroendoscope. We performed cylinder surgery with a transparent sheath under observation with a rigid neuroendoscope.**

■ RESULTS: **Neuroendoscopic biopsies were performed in 11 patients, and resections were performed in 9 patients. All lesions were observed with a neuroendoscope under sequential white light and violet light. We confirmed the presence of a red fluorescent lesion under violet light in 15 patients, including 4 of 5 glioblastoma cases (80%); 1 of 2 anaplastic astrocytoma cases (50%); 4 of 5 diffuse large B cell lymphoma cases (80%); 2 of 2 metastatic brain tumors; 1 of 1 case each of diffuse astrocytoma, pilocytic astrocytoma, inflammatory change, and germinoma (100%); and no cases of anaplastic ependymoma or cysticercosis. Pretargeted lesions were accurately harvested from all biopsy specimens. Gross total resection was achieved in 5 of 9 patients using a resection procedure.**

■ CONCLUSIONS: **Our described method offers a promising technique for achieving precise brain tumor biopsies and safe resection.**

INTRODUCTION

Intraoperative use of the fluorescent biomarker 5-aminolevulinic acid (5-ALA) clearly enables surgeons to visualize brain tumors and facilitates their removal. This technique has conventionally been used for the microscopic removal of malignant glioma. Gross total resection (GTR) of a malignant brain tumor has a notable influence on patient survival.[1,2] Furthermore, 5-ALA is also useful for the photodynamic diagnosis of low-grade gliomas, meningiomas, and metastatic brain tumors under a microscope, and researchers speculate that this technique could aid in the intraoperative identification of these tumors.[3]

In neuroendoscopic surgery, several case reports have described neuroendoscopic biopsy with photodynamic diagnosis (PDD) using 5-ALA fluorescence.[4-6] In 2014, Rapp et al.[7] reported 9 cases of neuroendoscopic PDD after microsurgical complete resection of

Key words
- 5-Aminolevulinic acid
- Brain tumor
- Neuroendoscopy
- Transparent sheath

Abbreviations and Acronyms
5-ALA: 5-Aminolevulinic acid
CT: Computed tomography
DLBCL: Diffuse large B cell lymphoma
GBM: Glioblastoma
LED: Light-emitting diode
MEP: Motor evoked potential
MRI: Magnetic resonance imaging
PDD: Photodynamic diagnosis
PR: Partial resection
SEP: Somatosensory evoked potential
VL: Violet light
WL: White light

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Citation: World Neurosurg. (2018) 116:e35-e41.
https://doi.org/10.1016/j.wneu.2018.03.112

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

the fluorescent tumor tissue.[7] They confirmed positive fluorescence under neuroendoscopic visualization in all cases, and histopathologic analysis of samples taken from the additional endoscopic procedures detected fluorescent areas confirmed as tumor tissue or necrosis in all patients. They suggested that the combination of endoscopic visualization and fluorescence-guided resection might overcome some of the technical limitations of conventional 5-ALA visualization.

To compare the conventional neuroendoscopic technique with the 5-ALA fluorescence neuroendoscopic technique, we used a neuroendoscope without a microscope and report the utility of an exclusively neuroendoscopic procedure with 5-ALA PDD in 20 cases of intracranial deep-seated lesions. We also provide detailed descriptions of a new device for PDD and the features of our original neuroendoscopic procedure.

MATERIALS AND METHODS

We retrospectively reviewed the records of 20 consecutive patients who were initially diagnosed with deep-seated intracranial malignant brain tumors. All patients underwent a tumor biopsy or tumor resection surgery between July 2016 and November 2017. Informed consent for surgery and publication of the results in our article was obtained from each patient.

Preoperative Evaluation

All patients underwent preoperative magnetic resonance imaging (MRI), including plain imaging (T1- and T2-weighted) and T1-weighted imaging following the injection of contrast medium. The location, maximum size, and number of tumors were evaluated. Information regarding the surrounding vasculature was also obtained using preoperative 3-dimensional computed tomography (CT). If multiple intracranial lesions were present, the largest lesion was considered the targeted lesion. We performed biopsies of intracranial lesions that were clinically suspected to be lymphomas or germ cell tumors. Patients who were considered intolerant of general anesthesia because of their characteristics or history underwent biopsy procedures. We performed biopsy or partial resection (PR) of lesions suspected to be gliomas located in eloquent brain regions on MRI; otherwise, tumor resection was performed. Preoperative neurologic examination findings were also assessed at admission.

Surgical Procedure

Each patient received a 20-mg/kg oral dose of 5-ALA dissolved in water 3 hours before the operation. After the induction of general anesthesia using endotracheal intubation, patients were placed on the operating table with their heads fixed with surgical tape. As necessary, motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) were elicited from each patient. A burr hole was made for biopsies, and a small craniotomy was introduced for resection. A corticotomy was performed in the noneloquent cortex. After the direction of approach to the lesion was determined with an electromagnetic neuronavigational system (StealthStation; Medtronic, Minneapolis, Minnesota, USA), a 15-cm–long transparent acryl puncture needle with a 5-mm outer diameter[7] was gently inserted into the burr hole toward the lesion under observation with a 2.7-mm 0° rigid neuroendoscope (EndoArm HD; Olympus, Tokyo, Japan). A light-emitting diode (LED; Aladuck LS-DLED; SBI Pharmaceuticals, Tokyo, Japan) delivering either white light (WL) or 400- to 410-nm violet light (VL) was attached to the neuroendoscope. A long-pass filter (SBI Pharmaceuticals, Tokyo, Japan) was positioned between the ocular lens of the neuroendoscope and the head of the camera to limit light with a wavelength less than 450 nm. The WL and VL could be changed easily with the foot switch connected to the LED emission source (Figure 1). Furthermore, a neuronavigational pointer (StealthStation EM Flexible Stylet; Medtronic) could be inserted into the needle to indicate the depth and direction of the needle. For patients undergoing biopsies, we removed the needle after identifying the lesion, inserted a transparent sheath with a diameter of 6.8 mm (NeuroPort Mini; Olympus, Tokyo, Japan) into the same tract, and subsequently inserted the neuroendoscope along the sheath. While watching the monitor, tumor tissues were harvested in a piecemeal manner using small forceps. For patients receiving resections, a transparent sheath with a diameter of 10 mm (NeuroPort; Olympus, Tokyo, Japan) was inserted along the tract. Tumor resection was performed with forceps and suction under neuroendoscopic visualization. If necessary, a sucker (Irrigation Sucker for endoscope; Fujita Medical Instruments, Tokyo, Japan) that was connected with monopolar cautery could be inserted into a 10-mm–diameter sheath and used as the probe of the direct cortical stimulator for lesions located in or near the motor area. After the procedure, thin bipolar forceps (Fujita Medical Instruments, Tokyo, Japan) were used for hemostasis in a 6.8- or 10-mm sheath (Figure 2).

Postoperative Evaluation

All patients underwent CT to assess postoperative hemorrhages within 24 hours after the operation. Postoperative MRI was performed within 1 week. In resection cases, T1-weighted non–contrast-enhanced and contrast-enhanced images were evaluated for each patient before and after the operation. The rate of tumor removal was calculated, and removal was classified as GTR, subtotal resection (>95%), or PR. A histopathologic examination was conducted to obtain the final diagnosis for each patient. Surgical outcomes were evaluated within 72 hours after the operation. Patients who exhibited new-onset neurologic deterioration were considered to have a poor outcome. Adverse effects owing to 5-ALA administration were also evaluated according to the medical package insert.

RESULTS

In total, 10 male and 10 female subjects with a mean age of 54.7 years (range, 8–77 years) were included in the study. The lesions scheduled to undergo surgery were in the following locations: frontal lobe (n = 4), temporal lobe (n = 5), parietal lobe (n = 4), occipital lobe (n = 2), thalamus (n = 3), and cerebellum (n = 2). The preoperative tumor size was 11.49 cm^3 (range 0.11–53.02 cm^3). The surgical methods consisted of 11 biopsies and 9 resections. Tumors were diagnosed histologically diagnosed as glioblastoma (GBM) in 5 patients, anaplastic astrocytoma in 2 patients, diffuse astrocytoma in 1 patient, pilocytic astrocytoma in 1 patient, anaplastic ependymoma in 1 patient, diffuse large B cell

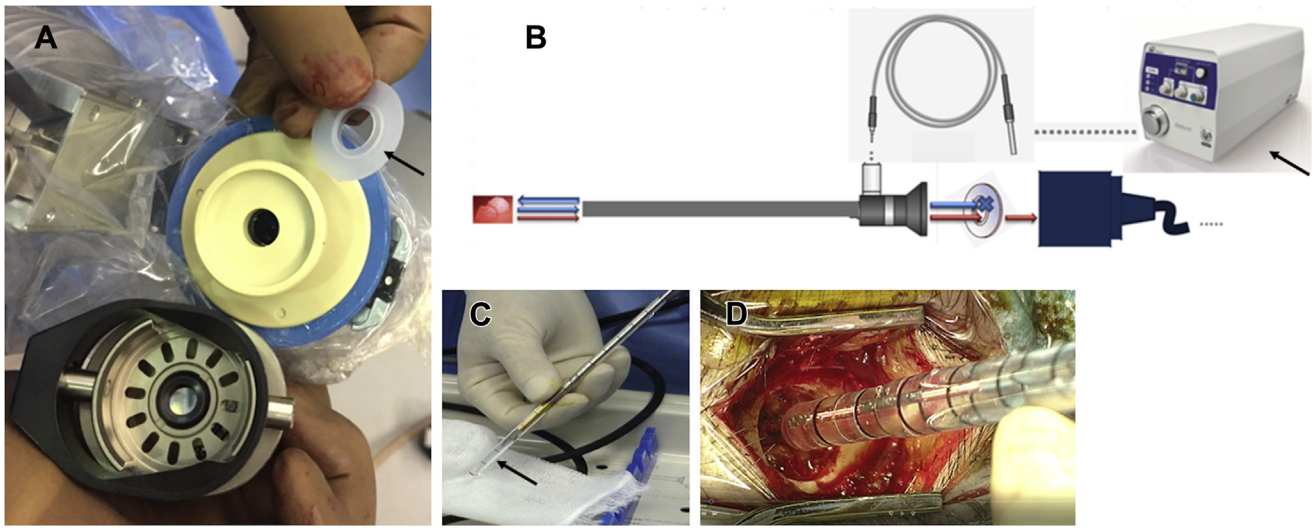

Figure 1. Layout of the surgical equipment for the neuroendoscopic 5-aminolevulinic acid (5-ALA) photodynamic diagnosis. (**A**) This method used a long-pass filter (*black arrow*) and neuroendoscope. (**B**) Schematic illustration of the 5-ALA–induced fluorescence neuroendoscopic system. A light-emitting diode (*black arrow*) delivering either white or 400–410-nm violet light was attached to the neuroendoscope. (**C**) A 2.7-mm 0° rigid neuroendoscope was inserted into a 15-cm–long transparent acryl puncture needle with a 5-mm outer diameter. (**D**) A transparent acryl puncture needle was gently inserted into the burr hole toward the lesion as directed by the electromagnetic neuronavigational system.

lymphoma (DLBCL) in 5 patients, metastatic brain tumors in 2 patients, germinoma in 1 patient, inflammatory changes in 1 patient, and cysticercosis in 1 patient. All lesions were observed with a neuroendoscope under sequential WL and VL. Fifteen specimens fluoresced with VL. Intraoperative 5-ALA fluorescence was observed in 4 of 5 GBM cases (80%); 1 of 2 anaplastic astrocytoma cases (50%); 4 of 5 DLBCL cases (80%); 2 of 2 metastatic brain tumors; 1 of 1 case each of diffuse astrocytoma, pilocytic

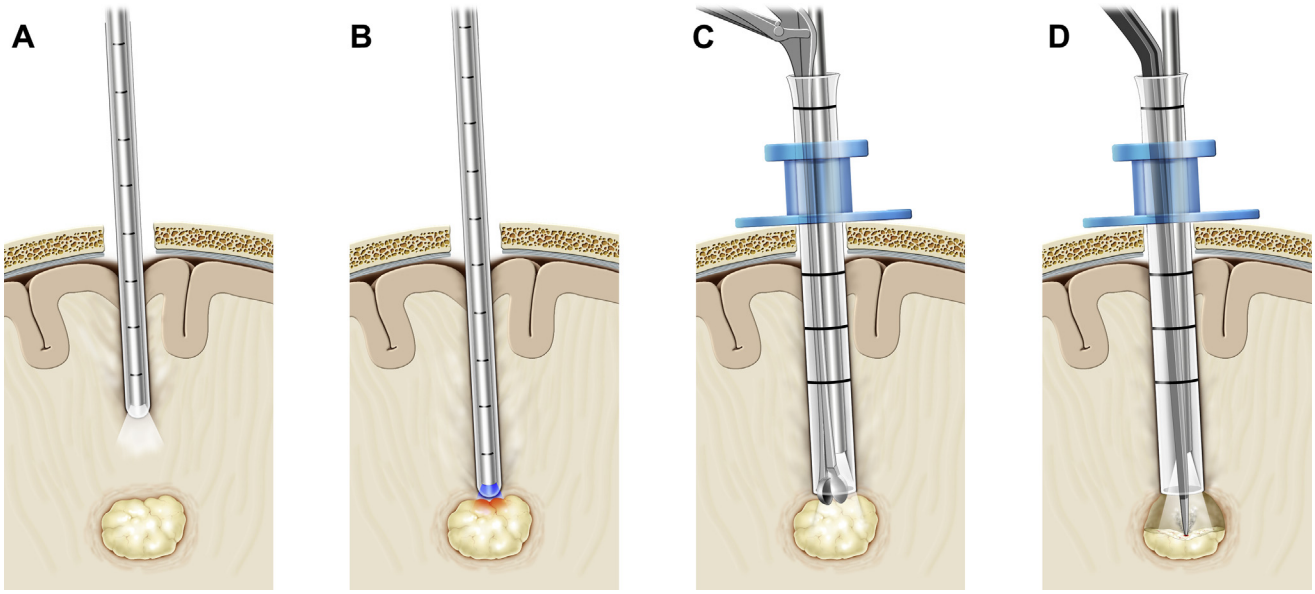

Figure 2. Schemata for neuroendoscopic 5-aminolevulinic acid photodynamic diagnosis and tumor resection. (**A**) A transparent acryl puncture needle was inserted toward the lesion under white light with a 2.7-mm 0° rigid neuroendoscope. (**B**) The red fluorescent tumor is shown under violet light through the needle. (**C**) After a transparent sheath with a diameter of 6.8 or 10 mm was inserted into the same tract, the tumor was harvested or resected with forceps. (**D**) Thin bipolar forceps (Fujita Medical Instruments, Tokyo, Japan) were used for hemostasis.

astrocytoma, inflammatory change, and germinoma (100%); and no cases of anaplastic ependymoma or cysticercosis (Table 1).

Lesions were classified into 3 groups according to the fluorescence pattern:

- WL(+)VL(+): the lesion was discriminated from the surrounding normal brain tissue under WL and emitted red fluorescence under VL.
- WL(+)VL(−): the lesion was discriminated from the surrounding brain tissue under WL but did not emit red fluorescence under VL.
- WL(−)VL(+): the lesion was not discriminated under WL but emitted red fluorescence under VL.

Ten patients were classified into the WL(+)VL(+) group, 5 patients were classified into the WL(+)VL(−) group, and 5 patients were classified into the WL(−)VL(+) group (Figure 3). Of the 11 patients undergoing biopsy, 4 patients (36%) were classified into the WL(+)VL(+) group, 3 patients (27%) were classified into the WL(+)VL(−) group, and 4 patients (36%) were classified into the WL(−)VL(+) group. Of the 9 patients undergoing resection, 6 patients (67%) were classified into the WL(+)VL(+) group, 2 patients (22%) were classified into the WL(+)VL(−) group, and 1 patients (11%) was classified into the WL(−)VL(+) group.

Eight of the 11 biopsy specimens were comfortably harvested from a red fluorescent lesion. However, targeted tissues were accurately harvested from the remaining 3 biopsy specimens with negative fluorescence under VL under neuroendoscopic observation with WL. Pretargeted lesions were harvested accurately from all biopsies.

GTR was achieved in 5 of 9 patients who underwent a resection procedure. We did not use MEPs or SEPs in any biopsy cases, but MEP was adapted in 1 case (patient number 11 in Table 1), and MEP and SEP in 1 case (patient number 13). The surgery resulted in subtotal resection in 1 patient because the SEPs had a low amplitude during the procedure. The surgery resulted in PR in the remaining 3 patients. In 1 patient (patient number 11), the lesion was partially located in the motor area, and intraoperative MEPs had a low amplitude. In another patient (patient number 18), the lesion was partially located in the corpus callosum, and the surgery resulted in PR. In the other patient (patient number 6), intraoperative pathologic diagnosis

Table 1. Patient Characteristics

Patient Number	Age (Years)	Sex	Tumor Type	Tumor Location	Surgical Method	Preoperative Volume (cm^3)	Volume (cm^3)	WL	VL
1	30	F	AA	Thalamus	Biopsy	0.11		+	−
2	66	F	DLBCL	Thalamus	Biopsy	3.55		+	+
3	66	F	DLBCL	Temporal	Biopsy	53.02		−	+
4	77	F	GBM	Temporal	Biopsy	2.92		−	+
5	71	M	DLBCL	Parietal	Biopsy	38.7		+	+
6	72	F	PA	Cerebellum	PR	5.47	1.2	+	+
7	24	M	Germinoma	Thalamus	Biopsy	3.96		+	+
8	50	F	Metastatic brain tumor	Temporal	GTR	0.74	0	−	+
9	54	M	DLBCL	Frontal	Biopsy	6.33		+	−
10	69	F	Inflammatory change	Temporal	Biopsy	8.38		−	+
11	74	M	GBM	Frontal	PR	3.40	1.13	+	+
12	42	M	GBM	Occipital	GTR	14.00	0	+	+
13	51	F	Cysticercosis	Parietal	Subtotal resection	0.60	0.02	+	−
14	66	M	DLBCL	Temporal	Biopsy	5.10		+	+
15	72	M	GBM	Parietal	Biopsy	7.40		+	−
16	74	F	AA	Parietal	Biopsy	8.45		−	+
17	34	M	DA	Occipital	GTR	0.68	0	+	+
18	49	M	GBM	Frontal	PR	50.18	39.09	+	+
19	8	M	Anaplastic ependymoma	Frontal	GTR	9.8	0	+	−
20	45	F	Metastatic brain tumor	Cerebellum	GTR	6.94	0	+	+

WL, white light; VL, violet light; AA, anaplastic astrocytoma; DLBCL, diffuse large B cell lymphoma; GBM, glioblastoma; PA, pilocytic astrocytoma; PR, partial resection; GTR, gross total resection; DA, diffuse astrocytoma.

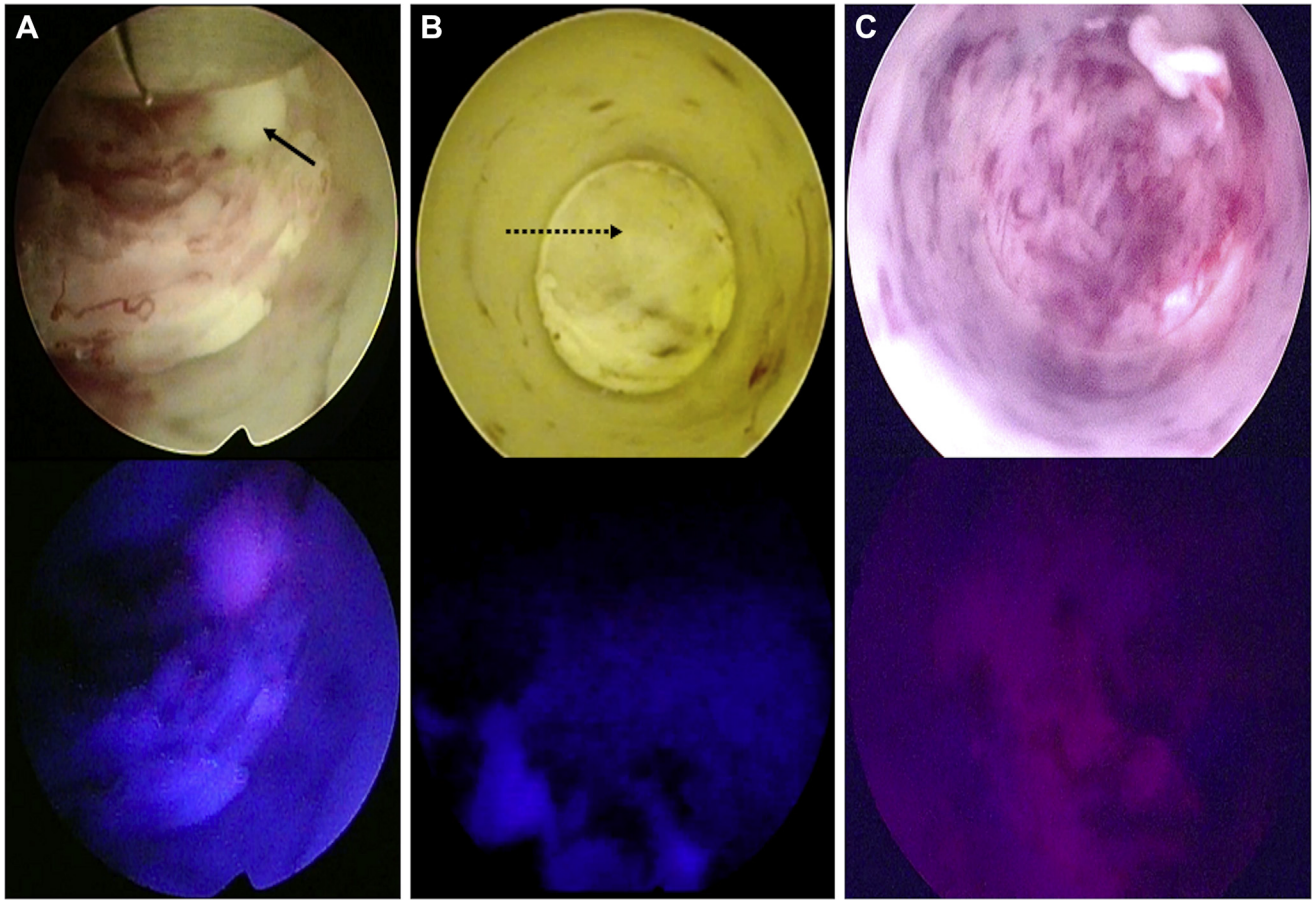

Figure 3. Fluorescent patterns observed under white light (WL) and violet light (VL). (**A**) WL(+)VL(+) specimen from patient number 5 in Table 1. The tumor was visible under WL (*black arrow*) and fluoresced under VL. (**B**) WL(+)VL(−) specimen from patient number 9 in Table 1. The tumor was visible under WL (*black dotted arrow*), but it could not be identified under VL. (**C**) WL(−)VL(+) specimen from patient number 16 in Table 1. Although the tumor was difficult to discriminate from the normal brain tissue under WL, the tumor was identified under VL.

revealed pilocytic astrocytoma, and we discontinued resection to avoid negative postoperative effects.

During the postoperative period, none of the patients who underwent biopsies displayed neurologic deterioration. One patient with cysticercosis located in the left post central gyrus presented a transient sensory disorder. Postoperative CT imaging did not reveal intracranial hemorrhages in any patient. None of the patients had any complications resulting from 5-ALA administration.

DISCUSSION

Visualization of Brain Tumors with 5-ALA

Preoperative oral administration of 5-ALA improves the intraoperative visualization of a tumor with a VL source.[3] Since Stummer et al.[8-11] reported the utility of fluorescence-guided resection with 5-ALA for GBM, 5-ALA has been recognized as an objective tool for assessing tumor infiltration, and it has been used as a neurosurgical adjunct to help discriminate neoplastic and normal brain tissues during tumor resection via microscopy.[8-11] In recent years, interest in the assessment of 5-ALA as a promising intraoperative adjunct for detecting non-GBMs has increased. Marbacher et al.[3] reviewed 22 case series involving 1163 patients who underwent microscopic surgery and found that the greatest 5-ALA sensitivity was observed for high-grade gliomas (85%), moderate sensitivity was observed for metastases (54%), and low sensitivity was observed for low-grade gliomas (16%). For primary central nervous system lymphoma, previous reports showed positive fluorescence rates, ranging from 73% to 82.9%. The histopathology results revealed DLBCL in most of these cases.[12,13]

Regarding neuroendoscopic PDD, 3 case reports of neuroendoscopic biopsies using 5-ALA fluorescence imaging for malignant gliomas and germ cell tumors have been published.[4-6] Rapp et al.[7] also reported neuroendoscopic PDD and additional resection after microsurgical complete resection of the fluorescent tumor tissue. In their report, 8 of 9 lesions exhibited strong fluorescence in the 5-ALA mode of the surgical microscope, and in all cases, additional fluorescent tissue could be

detected by endoscopic visualization of the resection cavity. Histopathologic examination revealed a malignant glioma in 6 patients, a newly diagnosed cerebral metastasis in 1 patient, a ganglioglioma in 1 patient, and radiation necrosis in 1 patient[7] (Table 2). We performed 5-ALA PDD for other types of lesions and found that 5-ALA fluorescence was positive in 4 of 5 GBM cases (80%), 1 of 2 anaplastic astrocytoma cases (50%), and 2 of 2 metastatic brain tumors (100%), which is similar to the results of Rapp et al.[7] Furthermore, we found that the 5-ALA fluorescence rate under neuroendoscopy was as high as the rate observed in previous reports using microscopy.

Of the 11 biopsy cases, 4 patients (36%) were categorized into the WL(+)VL(+) group, 3 patients (27%) were categorized into the WL(+)VL(−) group, and 4 patients (36%) were categorized into the WL(−)VL(+) group. These results indicate that we could identify the existence of lesions under a conventional neuroendoscope with illumination with conventional WL in 7 patients. In the 4 remaining patients, we could discriminate tumors from normal brain tissue under VL. Therefore, we could accurately harvest tissue in all biopsies. Of the 9 resection cases, 6 patients (67%) were categorized into the WL(+)VL(+) group, 2 patients (22%) were categorized into the WL(+)VL(−) group, and 1 patients (11%) was categorized into the WL(−)VL(+) group. We could achieve additional resection of residual lesions under VL after conventional WL in 6 patients. The 2 cases in the WL(+)VL(−) group included cysticercosis and anaplastic ependymoma. No reports have described detection of 5-ALA fluorescence using a microscope or an endoscope. Only one resection case (patient number 8) was classified into the WL(−)VL(+) group; however, GTR may be difficult to achieve under conventional WL without VL instruments. Therefore, we emphasize that the use of 5-ALA with a neuroendoscope could contribute to radical tumor removal because in many WL(−)VL(+) cases, surgeons cannot easily discriminate lesions from normal brain tissue. However, VL fluorescence was not observed in 5 of 20 cases. Therefore, VL(−) findings should be interpreted with caution.

Interestingly, we observed positive fluorescence in a case displaying inflammatory changes (n = 1) and negative fluorescence in a case of cysticercosis (n = 1). A previous study found notable inflammatory cell infiltration in pseudopositive specimens, indicating that protoporphyrin IX or 5-ALA likely leaked through the damaged blood–brain barrier and passed into the inflammatory cells.[14] As no report on 5-ALA PDD for cysticercosis has been published, we describe new findings of negative 5-ALA fluorescence in cysticercosis.

Advantages of Our Newly Developed Procedure

Although stereotactic procedures are often performed for tumor biopsy in neurosurgery, blind procedures carry a risk of hemorrhagic complications.[15] In neuroendoscopic surgery, however, the monopolar or bipolar coagulation technique for arterial bleeding and tamponade with hemostatic agents and warm saline irrigation for venous bleeding can be adopted under neuroendoscopic visualization.[16-18] The same is true for microscopic procedures using a similar translucent tubular retractor; however, compared with microscopic procedures, the greatest advantage of the neuroendoscope is that it offers close and panoramic surgical views with fine illumination,[19] even in the deep intracranial area. A 0° endoscope or an oblique-viewing endoscope can be inserted into the sheath for visualization of the cavity so that surgeons can observe lesions in blind areas. If residual lesion remains, the sheath can be inclined by a small angle, and subsequent further resection can be achieved.

Furthermore, we used a transparent puncture needle that was safely inserted with the neuroendoscope. We were able to view intracranial structures, such as the white matter, small vessels and tumor tissues, through the clear needle tip. Moreover, the thin bipolar forceps specialized for neuroendoscopic cylinder surgery, which were presented in our previous report,[20] were particularly useful in 6.8- and 10-mm diameter sheaths. Because we used these techniques and instruments, postoperative intracranial hemorrhaging was not detected in any patient in the present series. We also found that a sucker for and endoscope that is connected with monopolar cautery can be used as the probe of the direct cortical stimulator, which allows surgeons to access the motor area.

Several reports have described the neuroendoscopic resection of brain tumors.[21] However, no reports have been published on exclusively neuroendoscopic resection with 5-ALA PDD. Tumors are often more difficult to distinguish from normal brain tissue under a neuroendoscope than under a microscope, which is a limitation to their performance. Moreover, during neuroendoscopic tumor biopsies or resections, surgeons might not be

Table 2. Summary of Previously Reported Neuroendoscopic Visualization with 5-ALA

References	Number of Patients	Tumor Type	Rate of Positive Fluorescence
Tamura et al., 2007[6]	1	Anaplastic astrocytoma	1/1 (100%)
Ritz et al., 2011[4]	1	Anaplastic oligodendroglioma	1/1 (100%)
Rapp et al., 2014[7]	9	Malignant glioma	6/6 (100%)
		Ganglioglioma	1/1 (100%)
		Radiation necrosis	1/1 (100%)
		Cerebral metastasis	1/1 (100%)
Takeda et al., 2017[5]	2	Mixed germ cell tumor	2/2 (100%)

able to distinguish tumors from normal brain tissues easily. Typically, neurosurgeons can identify tumors on the basis of visual and haptic information. However, in neuroendoscopic cylinder surgery, haptic information is more difficult to obtain than in microscopic surgery because of the strong interference between surgical instruments and the neuroendoscope or cylinder. Therefore, neurosurgeons are likely to resect tumors only using visual information under a neuroendoscope. However, 5-ALA PDD helps neurosurgeons to identify tumors by reinforcing the visual information. In fact, 5 of the 20 cases in the current series were classified as WL(−)VL(+), in which the tumors were difficult to distinguish from the normal brain tissue under WL alone. In these cases, red fluorescence under VL led to a more accurate tumor biopsy and more radical tumor resection. We suggest that 5-ALA PDD represents an essential adjunct in neuroendoscopic cylinder surgery for brain tumors.

CONCLUSION

We performed PDD as an accurate and safe procedure using 5-ALA neuroendoscopy. Although no reports of neuroendoscopic brain tumor resection with 5-ALA have been published, the technique is efficacious for visualizing lesions that cannot be discriminated under WL and for confirming residual lesions. In the future, a broader investigation of various tumors will be necessary. We believe that this technique represents a promising method for accurate and safe biopsies and resection of brain tumors.

ACKNOWLEDGMENTS

The authors thank Kiyotaka Murakami for providing timely assistance and supplying the LED source.

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Received 25 December 2017; accepted 15 March 2018

Citation: World Neurosurg. (2018) 116:e35-e41.
https://doi.org/10.1016/j.wneu.2018.03.112

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1878-8750/$ - see front matter