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Photodynamic therapy using talaporfin sodium for non-totally resectable malignant glioma

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ABSTRACT

Background: For malignant glioma, intraoperative photodynamic therapy (PDT) using talaporfin sodium is a powerful tool for local tumor control, when gross total removal is performed. However, the efficacy of PDT for non-totally resectable malignant glioma has not been clearly confirmed. Therefore, the purpose of this study was to clarify the usefulness of PDT using talaporfin sodium for non-totally resectable malignant glioma.

Methods: Eighteen patients with malignant glioma (16 new onset, 2 recurrent) in whom gross total removal was judged to be difficult from the images obtained before surgery were evaluated. Fifteen patients had glioblastoma (14 newly diagnosed, 1 recurrent), and 3 patients had anaplastic oligodendroglioma (2 newly diagnosed, 1 recurrent). The whole resection cavity was subjected to PDT during the surgery. For newly diagnosed glioblastoma, postoperative therapy involved the combined use of radiation and temozolomide. Bevacizumab treatment was also started at an early stage after surgery.

Results: In some patients, reduction of the residual tumor was observed at an early stage of chemoradiotherapy after the surgery, suggesting the positive effect of PDT. Recurrence occurred in 15 of the 18 patients during the course of treatment. Distant recurrence occurred in 8 of these 15 patients, despite good local tumor control. In the 14 patients with newly diagnosed glioblastoma, the median progression-free survival was almost 10.5 months, and the median overall survival was almost 16.9 months.

Conclusions: PDT for malignant glioma is expected to slightly improve local tumor control for non-totally resectable lesions.

1. Introduction

Malignant glioma, such as glioblastoma and anaplastic astrocytoma, has an unfavorable prognosis, with a mean survival time of patients of less than 2 years. The resection rate of malignant glioma is thought to affect patient prognosis. Therefore, the location of the lesion is a prognostic factor. Intraoperative photodynamic therapy (PDT) using talaporfin sodium (TPS, Laserphyrin®, Meiji Seika Pharma Co., Ltd.) for malignant glioma has been reported to be effective both in the experimental and clinical setting. A phase II study testing the effects of PDT using TPS in patients with malignant brain tumors, including glioblastoma (GBM) (59.1 % of patients) reported outstanding results, in which the 12-month overall survival, 6-month progression-free survival (PFS), and 6-month local PFS after PDT were 95.5 %, 91 %, and 91 %, respectively [1]. With these results, PDT using TPS for the treatment of primary intracranial malignant tumors was approved in Japan for health insurance coverage, and this therapy has gradually become widespread in Japan. The depth of delivery of a 664-nm laser to the brain is speculated to be approximately 4 to 5 mm in the normal brain, and approximately 10 mm in edematous brain structures in regions of tumor invasion [2]. According to our data from 3 brain autopsies, the histopathological changes of tissues in the PDT area occur in regions of 9 to 18 mm in depth [3]. Therefore, PDT is expected to improve the local control of lesions that cannot be totally resected by surgery. Nitta et al. reported excellent treatment results of PDT for newly diagnosed glioblastoma, with a median overall survival of 27 months. In that study, the tumor extraction rate was an average of 98 %, and the data was from patients with totally resectable tumors [4]. A phase II study also demonstrated a greater than 90 % removal rate of all newly diagnosed glioblastomas [1]. Our cases of patients undergoing PDT for newly diagnosed glioblastoma demonstrated that when the extraction rate is more than 95 %, the median overall survival (mOS) is favorable, at

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approximately 22 months (data not shown). However, the efficacy of PDT for patients with subtotal or partial tumor resection remains unclear at present. Therefore, the aim of this study was to clarify the efficacy of PDT using TPS for non-totally resectable malignant glioma.

2. Materials and methods

2.1. Patients, surgical procedures, and postoperative therapy

Among the 121 patients with malignant glioma who underwent tumor resection in combination with PDT at Tokyo Medical University hospital, 18 patients in whom gross total removal of the tumor was judged to be difficult from images obtained before surgery were analyzed from 2014 to 2022. The details are described in Table 1. Tumor size and response to treatment were evaluated using the Response Assessment in Neuro-Oncology Criteria (RANO) classification. The mean age of the patients was about 52 years (30 to 74 years), and the mean maximum size of the tumor was about 61 mm (27 mm to 102 mm). All patients underwent PDT after the procedure became covered by public health insurance in Japan. There were 16 patients with newly onset disease, and 2 patients with recurrent disease. According to the pathological diagnosis of the World Health Organization 2016, 15 patients had grade IV (14 newly onset, 1 recurrent), and 3 patients had grade III (anaplastic oligodendroglioma, *isocitrate dehydrogenase (IDH)-mutant and 1p/19q-codeleted*, 2 newly onset and 1 recurrent) glioma. The details of the patients are described in Table 1. Lesions were located in the deep part of the basal ganglia, primary motor area, pyramidal tract, and arcuate fasciculus. The entire resection cavity was subjected to PDT during the surgery (2–16 times). To avoid duplicate irradiation and irradiation of the main artery and large vein, cotton sheets sandwiched with aluminum foil (PDT sheet®, Yufu Itonaga Co., Ltd., Tokyo, Japan) were used to cover these areas. Irradiation using a mirror (PDT mirror®, Yufu Itonaga Co., Ltd.) which was a technique developed by our department, was performed on the blind spots that could not be irradiated by conventional PDT, such as narrow corridor and overhang regions [5]. The maximum length of the residual tumor was recorded by MRI within 7 days after the surgery. For patients with newly diagnosed glioblastoma, postoperative adjuvant therapy involved the combined use of radiotherapy (RT) and temozolomide (TMZ). Bevacizumab (BEV) treatment was started at an early stage after surgery. In a recent case, novel antimitotic-based tumor treating fields was performed at the patient's request. For patients with anaplastic oligodendroglioma, postoperative adjuvant therapy was combined with RT and procarbazine-ACNU-vincristine therapy (PAV), RT and TMZ, or only PAV. To compare the prognosis of newly diagnosed glioblastomas, we analyzed 14 cases of patients with non-totally resectable grade IV glioblastoma who did not undergo PDT but underwent surgery at our institution from 2009 to 2020. The reasons for not performing PDT included the lack of insurance coverage, and the judgment of the physician in charge. The patients included those receiving interferon and PAV therapy in addition to TMZ and BEV as adjuvant therapy. The mean age and the mean maximum size of the tumor were 65 years and 60 mm, respectively.

2.2. Statical analysis

Statistical analyses of median progression-free survival (mPFS) and mOS were performed using GraphPad Prism 5 software (GraphPad Software, Inc. La Jolla, CA, USA). Differences between 2 groups, such as age and tumor size, and differences in survival status were analyzed using the Mann-Whitney test and log-rank test, respectively. Spearman's correlation coefficient was used to assess the correlation between the size of residual tumors and mPFS/mOS. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

The details and disease course of all of the patients are shown in Table 1. The extent of tumor removal was subtotal removal (80 %–94 %) in 9 patients, and partial removal (20 %–79 %) in 9 patients. Various definitions of the degree of tumor removal have been reported [6]. In this study, we defined the degree of removal as described above based on a comparison of preoperative and postoperative contrast-enhanced lesions of magnetic resonance imaging (MRI) for enhanced tumors. Grade III tumors without contrast were identified as having a high signal on fluid-attenuated inversion recovery (FLAIR) MRI. There were no adverse events caused by the PDT. When residual tumor was observed after the Stupp's regimen in patients with a newly diagnosed tumor, BEV was introduced at an early stage after surgery. In some patients, reduction of the residual tumor was observed at an early stage of chemoradiotherapy after the surgery, suggesting a positive effect of PDT. A total of 15 out of the 18 patients showed recurrence during the treatment course. Dissemination or distant recurrence occurred in 8 of the 15 patients, despite favorable local tumor control (patients 7, 9, 10, 11, 12, 14, 15, and 17). All but 1 patient survived for more than 10 months, including patients with grade IV tumor. For the 14 patients with newly diagnosed glioblastoma, the mPFS was almost 10.5 months, and the mOS was almost 16.9 months. The survival outcome was then compared with that of patients who were not treated by PDT (Table 2). mPFS was 2.5 months and mOS was 9.4 months in patients who were not treated with PDT. Although patients who did not undergo PDT were relatively older, had larger tumors, and underwent surgery at slightly different times, mPFS and mOS were comparatively better in patients who underwent PDT, although the difference was not statistically significant (Fig. 1). Regarding the patients who survived for more than 12 months, 69 % had undergone PDT and 28 % had not. When limited to the 10 patients who had already died, there was no statistically significant correlation between residual tumor size and mPFS and mOS (Spearman r: -0.39, $p = 0.26$ and Spearman r: -0.50, $p = 0.14$, respectively).

We encountered 3 cases of patients with grade III glioma (anaplastic oligodendroglioma, *IDH-mutant and 1p/19q-codeleted*). In 1 patient with recurrent disease, recurrence occurred locally after 24.7 months, and the patient died after 50.7 months. In the 2 newly diagnosed patients, the residual tumors with a high FLAIR signal shrank after surgery, although they did not disappear. However, the residual tumors showed no sign of regrowth 28 and 63 months after the surgery.

4. Three representative cases treated by PDT

4.1. Case 13: anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted

The patient was a 32-year-old woman. She developed loss of memory, slight aphasia, and numbness in the left lower extremity without motor weakness. A huge, partially contrast-enhanced lesion extending from the right frontal lobe to the corpus callosum was displayed on brain FLAIR MRI (Fig. 2A). The preoperative diagnosis was grade III glioma. Owing to the patient's insistence, radical total resection was not attempted. Immediately after the surgery (partial removal), the tumor in the corpus callosum and around the primary motor area of the right frontal lobe remained (Fig. 2B). She received chemotherapy with TMZ and RT (60 Gy, 30 fractions), because the pathological diagnosis was anaplastic oligodendroglioma, *IDH-mutant and 1p/19q-codeleted*, grade III. One month after the surgery, the residual tumor gradually shrank, and the patient was able to return to work (Fig. 2C). Six months after the surgery, the tumor had shrunk further and has not recurred for 28 months (Fig. 2D).

4.2. Case 14: glioblastoma, IDH-wild

The patient was a 46-year-old woman. She presented with mild

Table 1
Clinical features of the 18 patients with non-totally resectable malignant glioma treated by photodynamic therapy (PDT).

Case	Age (years)	Sex	New/ Rec	Location	Size (mm)	Pathology	PDT (mirror)	Remove	Residual tumor (mm)	Adjuvant Tx	RANO	PFS (months)	OS (months)	Recurrence pattern	Status
1	34	M	New	Lt basal ganglia	38	GBM, *IDH*-wild	×2	Partial (20 %–79 %)	31	RT+TMZ+BEV	PD	4.1	13.7	Local	Dead
2	59	M	New	Lt thalamus	66	GBM, NOS	×3	Partial (20 %–79 %)	45	RT+TMZ+BEV	CR	10.4	16.9	Local	Dead
3	68	F	New	Rt frontotemporal	91	GBM, *IDH*-wild	×4	Partial (20 %–79 %)	28	RT+TMZ	PD	0.7	12	Local	Dead
4	58	F	New	Lt parietal	56	GBM, *IDH*-wild	×5	Subtotal (80 %–94 %)	13	RT+TMZ	PR	11.3	24	Local	Dead
5	46	F	New	Lt temporal	74	AO, *IDH*-mutant	×4	Partial (20 %–79 %)	46	RT+PAV	PR	(−)	63	(−)	Alive
6	46	M	Rec	Rt temporal	102	AO, *IDH*-mutant	×4 (1)	Partial (20 %–79 %)	58	PAV	PR	24.7	50.7	Local	Dead
7	74	F	Rec	Rt parietal	56	GBM, *IDH*-wild	×9	Subtotal (80 %–94 %)	15	RT+TMZ+BEV	PR	14.5	18.9	Dis	Dead
8	69	M	New	Lt frontal	64	GBM, *IDH*-wild	×12	Subtotal (80 %–94 %)	51	RT+TMZ+BEV	PR	13	14.5	Local	Dead
9	69	F	New	Rt frontal	41	GBM, *IDH*-wild	×7(1)	Subtotal (80 %–94 %)	6	RT+TMZ+BEV	PR	16.7	21.8	Dis	Dead
10	46	M	New	Lt temporoparietal	62	GBM, *IDH*-wild	×5	Subtotal (80 %–94 %)	18	RT+TMZ+BEV	CR	10	15.6	Dis	Dead
11	68	M	New	Lt temporal	45	GBM, *IDH*-wild	x9	Subtotal (80 %–94 %)	27	RT+TMZ+BEV	CR	6	9.1	Dis	Dead
12	30	M	New	Lt occipital	55	GBM, *IDH*-mutant	×10	Subtotal (80 %–94 %)	24	RT+TMZ+TTF	CR	6.8	10.9	Dis	Dead
13	32	F	New	Rt frontal	95	AO, *IDH*-mutant	×16	Partial (20 %–79 %)	37	RT+TMZ	PR	(−)	28.0	(−)	Alive
14	46	F	New	Lt frontal	63	GBM, *IDH*-wild	×7 (1)	Subtotal (80 %–94 %)	19	RT+TMZ+BEV+TTF	CR	9.8	17	Dis	Alive
15	51	F	New	Lt temporoparietal	73	GBM, *IDH*-wild	×7	Subtotal (80 %–94 %)	27	RT+TMZ+BEV	PR	10.5	15.5	Dis	Alive
16	56	M	New	Rt frontal	51	GBM, *IDH*-wild	×5	Partial (20 %–79 %)	37	RT+TMZ+BEV	CR	16.3	18	Local	Alive
17	48	M	New	Lt frontal	27	GBM, *IDH*-wild	×4	Partial (20 %–79 %)	19	RT+TMZ+BEV+TTF	PR	15	17.5	Dis	Dead
18	40	M	New	Lt temporoparietal	53	GBM, *IDH*-wild	×7 (1)	Partial (20 %–79 %)	32	RT+TMZ+BEV	CR	(−)	11	(−)	Alive

Rt, right; Lt, left; M, male; F, female; New, newly diagnosed; Rec, recurrence; GBM, glioblastoma; NOS, not otherwise specified, AO, anaplastic oligodendroglioma; IDH, isocitrate dehydrogenase; RT, radiation therapy; TMZ, temozolomide; BEV, bevacizumab; PAV, procarbazine-ACNU-vincristine therapy; RANO, response assessment in neuro-oncology criteria; PD, progression; CR, complete response; PR, partial response; TTF, novel antimitotic-based tumor treating fields; Dis, dissemination or distant recurrence.

Table 2
Comparison of 28 non-totally resectable malignant glioma patients with or without PDT.

	PDT (+) (n = 14)	PDT (−) (n = 14)	p-value
Operation period (AD)	2014–2022	2009–2020	
Mean age (years)	52	65	0.03* Mann-Whitney test
Mean maximum size (mm)	56	60	0.59 Mann-Whitney test
Pathology			
GBM, *IDH*-wild	12	6	
GBM, *IDH*-mutant	1	0	
GBM, NOS	1	8	
Resection			
Partial (20 %–79 %)	6	8	
Subtotal (80 %–94 %)	8	6	
Treated with BEV	10	6	
mPFS (months)	10.5	2.6	0.43 log-rank test
mOS (months)	16.9	9.4	0.13 log-rank test

PDT, photodynamic therapy; GBM, glioblastoma; NOS, not otherwise specified, IDH, isocitrate dehydrogenase; BEV, bevacizumab; mPFS, median progression-free survival; mOS median overall survival; *, $p < 0.05$.

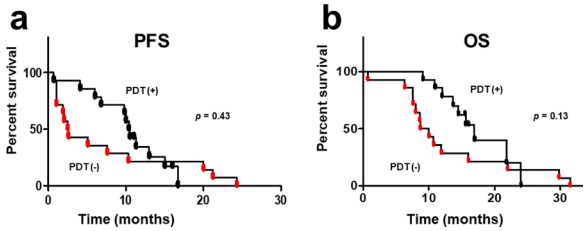

Fig. 1. Survival curve of PFS (a) and OS (b) of patients with non-totally resectable glioblastoma with or without PDT.
mPFS and mOS were comparatively better in patients who underwent PDT, although the difference was not statistically significant.

motor aphasia. Her initial MRI displayed a large ring-like enhanced mass in the left frontal lobe, with a small satellite lesion in the eloquent area that could not be removed (Fig. 3A). Immediately after the operation, the lesion posterior to the extraction cavity remained (Fig. 3B). However, the residual lesion disappeared 2 months after tumor removal (Fig. 3C). The patient had a favorable course, but 9.8 months later, she developed severe nausea. The brain MRI displayed no recurrence around the extraction cavity, but there was a small mass lesion around the fourth ventricle of the cerebellum, which appeared to be distant recurrence, suggesting dissemination of the glioblastoma cells (Fig. 3D). After additional radiotherapy of the cerebellum, tumor growth ceased. The patient remains alive 17 months after the operation.

4.3. Case 18: glioblastoma, IDH-wild

The patient was a 40-year-old man. He presented with personality changes and moderate aphasia. No motor paralysis was observed. An initial MRI displayed an irregular ring-like enhanced mass in the left temporal and parietal lobe, which could not be removed completely (Fig. 4A). Resection of the tumor was performed on the left temporal lobe lesion, whereas the parietal lobe tumor was not removed owing to the risk of motor paralysis. PDT was then performed on the residual lesions. Three days after the initial operation, we confirmed that the parietal tumor remained, although the temporal lesion had been removed (Fig. 4B). However, 18 days after the operation (8 days after the start of chemoradiotherapy), the temporal and parietal tumors had both nearly disappeared (Fig. 4C), indicating the favorable effect of PDT.

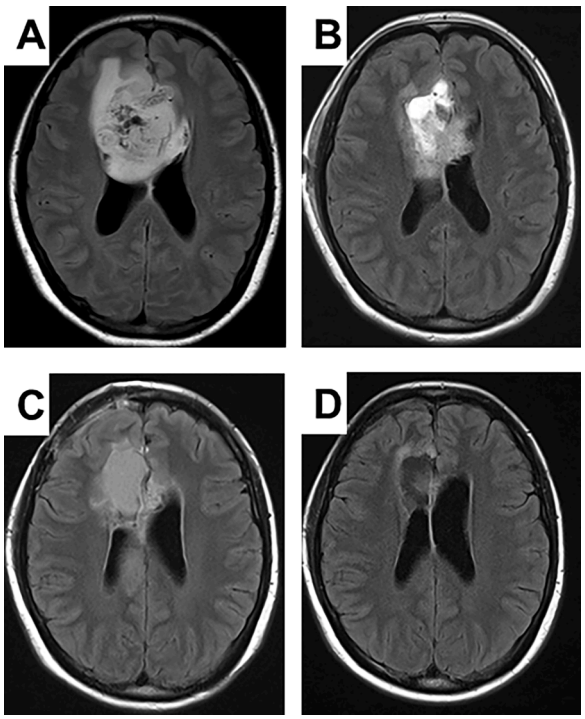

Fig. 2. Case 13 (32-year-old woman): anaplastic oligodendroglioma, *IDH-mutant and 1p/19q-codeleted*.
Preoperative FLAIR MRI (A) of patient 13 displaying anaplastic oligodendroglioma, *IDH-mutant and 1p/19q-codeleted*, in the patient's right frontal lobe to the corpus callosum, with infiltration into the primary motor area. Postoperative FLAIR MRI taken 3 days (B), 1 month (C), and 24 months (D) after the operation.

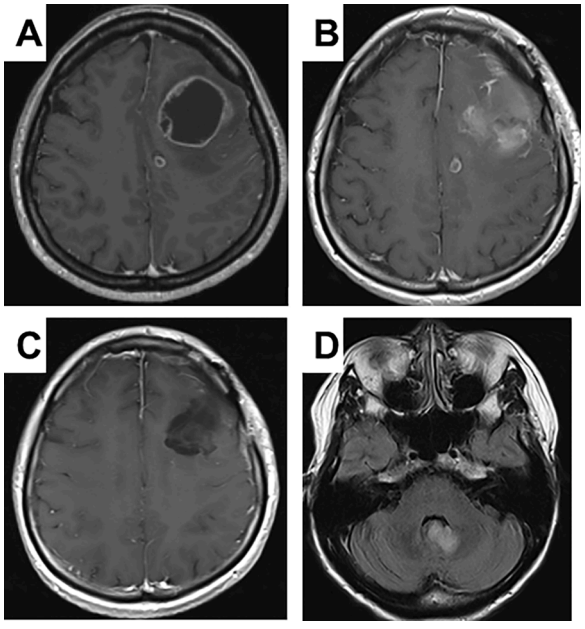

Fig. 3. Case 14 (46-year-old woman): glioblastoma, *IDH*-wild.
Preoperative gadolinium-enhanced brain MRI (A) of patient 14 displaying glioblastoma, *IDH*-wild, in the left frontal lobe with a satellite lesion near the primary motor area. Postoperative gadolinium-enhanced brain MRI taken 3 days (B) and 2 months (C) after the operation. Brain FLAIR MRI taken 9.8 months after the operation displayed a small mass lesion around the fourth ventricle of the cerebellum (D).

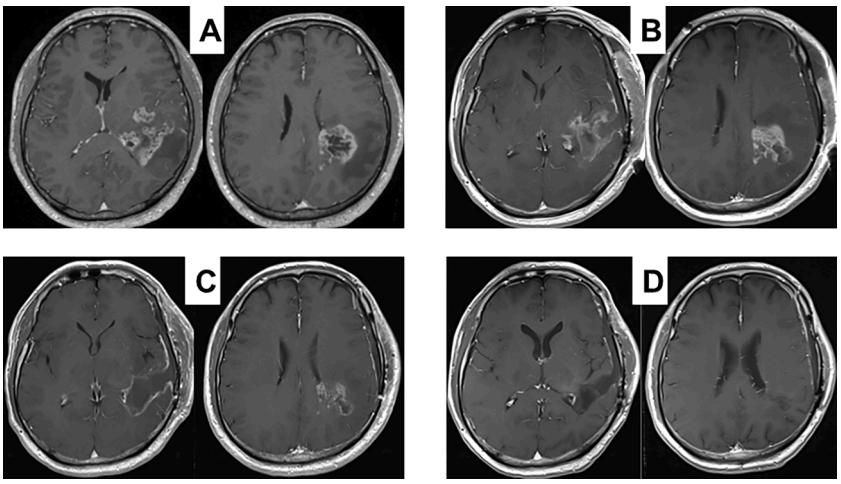

Fig. 4. Case 18 (40-year-old man): glioblastoma, *IDH*-wild.
Preoperative gadolinium-enhanced brain MRI (A) of patient 18, displaying glioblastoma, *IDH*-wild, in the left temporal and parietal lobe. Postoperative gadolinium-enhanced brain MRI taken 3 days (B), 18 days (C), and 2 months (D) after the operation.

After 2 months, all contrast-enhanced lesions had completely disappeared (Fig. 4D), and have not recurred for 11 months after the operation.

5. Discussion

In this study, the therapeutic effect of PDT on glioblastomas that were unable to be removed totally was investigated. The residual lesions in many patients gradually shrunk or disappeared. Although this phenomenon may have been caused by chemotherapy or radiotherapy after the operation, in some patients, such as patient 18, shrinkage of the tumor was observed with minimal use of TMZ and RT after the surgery, suggesting the favorable effect of PDT against the residual tumor. Therefore, PDT for malignant glioma is expected to improve local tumor control against unresectable lesions. Although the number of patients with newly diagnosed GBM was small (14 patients), mPFS was 10.5 months and mOS was 16.9 months. Although there was no statistically significant difference between the group that received PDT and the group that did not receive PDT owing to the small number of patients, both mPFS and mOS tended to be longer in the group that received PDT. In addition, the fact that there were 2 patients who did not receive PDT but who achieved long-term survival of more than 2 years may be another reason why the difference was not statistically significant. These 2 patients were initially treated more than 10 years previously, and their genetic changes in *IDH* have not been evaluated. In addition, both patients responded well to the initial treatment with a complete reaction, and may have hence been biologically chemotherapy-effective patients, such as having an *IDH* mutation or methylation of O6-methylguanine-DNA methyltransferase (*MGMT*). The survival rate for more than 12 months was predominantly higher for patients who received PDT (69 %) than for those who did not receive PDT (28 %), suggesting that PDT substantially contributes to early postoperative tumor control. The interpretation of the outcome differences between the 2 groups requires caution because the patients in the group that did not undergo PDT were older, their tumors were larger, and the timing of treatment was slightly different. In addition, there may have been a bias in patient selection, and thus this is not a satisfactory comparison. The longer PFS in the group of patients who underwent PDT may be owing to the early local tumor control by PDT, in addition to fewer patients with partial resection and a higher rate of bevacizumab use. The survival outcomes of patients who underwent PDT in our department was slightly more favorable than those from other institutions of patients treated with BEV/irinotecan/TMZ/RT for unresectable GBM (mPFS 7.1 months; mOS 11.1 months) [7]. Therefore, PDT may improve the prognosis of patients with newly diagnosed glioblastoma that cannot be resected totally. In the future, a prospective study with a larger number of patients matched for adjuvant therapy, *IDH* status, and *MGMT* methylation status is desirable. In the present study, no association between residual tumor size and prognosis was found. Although the reason remains unclear, it may be associated with the shape of the residual tumor, the site of the residual tumor, or other factors associated with the reach of laser irradiation. We cannot discuss the prognosis of grade III glioma because data on long-term follow-up was not available in this study. As even grade III gliomas, such as that of case 13, can be expected to shrink in a relatively short period of time, one strategy is to limit resection to only non-eloquent areas so as not to cause neurological symptoms.

Regarding the pattern of recurrence, the fact that distant and/or disseminated recurrence was more common (8/15) than local recurrence suggests that local control was achieved by PDT. Local recurrence was 63 % to 93 % with the Stupp regimen (TMZ+RT) [8–12], and 72.7 % to 80 % for the Stupp regimen with carmustine (BCNU) wafer [13–15]. Nitta et al. also demonstrated that the treatment of newly diagnosed glioblastoma with PDT combined with talaporfin sodium and total resection resulted in local recurrence in 58.8 % of the patients, with distant recurrence or dissemination being more common in 38.8 % [4]. Local recurrence has been reported to be more favorable than dissemination or distant recurrence in terms of prognosis, so preventing non-local recurrence is key for longer survival [16]. In basic science experiments, PDT-resistant glioma cells have increased migration and invasive capacity, so the pattern of recurrence after PDT may be more likely to be distant recurrence [17]. Therefore, when removing the tumor, it is necessary to avoid opening the ventricles as much as possible to prevent spinal fluid dissemination, and to perform ventriculoplasty when the ventricles are opened. In addition, Kobayashi et al. demonstrated that treatment with the mitogen activated protein kinase 1/2 inhibitor trametinib suppressed the enhanced migration and invasion of tumor cells, suggesting that the combination of PDT and trametinib may lead to a more favorable outcome. As a new irradiation method, the usefulness of interstitial PDT (iPDT), a procedure using 5-aminolevulinic acid (5-ALA) under fiber optics, has been reported as a minimally invasive method of PDT for unresectable GBM [18,19]. Because PDT using an optical fiber with talaporfin sodium is already covered by medical insurance in Japan for lung cancer and esophageal cancer, it is expected to be applied to malignant glioma in deep white matter lesions or brain stem lesions in the field of neurosurgery, which is difficult to treat with conventional microscopic surgery [20–22]. In the future, various types of PDT are expected to be performed, including our method and iPDT. The development of PDT alone as a method of local

tumor control is not sufficient for improving the outcome of malignant gliomas. Therefore, the establishment of new systemic treatment methods including PDT, such as molecular-targeted therapies and immunotherapies are desired.

6. Conclusion

In this study, the effect of PDT on glioblastomas that could not be removed totally was investigated. The residual lesions in many cases shrunk or disappeared gradually. In some cases, tumor shrinkage was observed in a situation in which TMZ and RT were used minimally after the surgery, suggesting the effect of PDT against the residual tumor. PDT for malignant glioma is expected to improve local tumor control against non-totally resectable lesions. The addition of PDT slightly improves survival prognosis, but a large improvement is not expected. Therefore, the establishment of new systemic treatment methods including PDT, such as molecular-targeted therapies and immunotherapies are desired. Further studies with a larger number of patients matched for adjuvant therapy, *IDH* status, and *MGMT* methylation status are needed to validate our results.

Ethical considerations

This study has been approved by the Medical Ethics Review Committee of Tokyo Medical University (study approval no.: T2020–0278).

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CRediT authorship contribution statement

Shinjiro Fukami: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jiro Akimoto:** Supervision. **Kenta Nagai:** Investigation, Data curation. **Yuki Saito:** Data curation. **Michihiro Kohno:** Supervision.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest in association with this study.

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