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Original Article

Photodynamic interstitial stereotactic therapy for recurrent malignant glioma

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ABSTRACT

Objectives: Stereotactic photodynamic therapy (sPDT) using 5-aminolaevulinic acid (5-ALA) as a cytotoxic photosensitizer may be a potentially prospective treatment option for malignant gliomas.

Material and Methods: We analyzed data from 10 patients with recurrent malignant gliomas of the brain who were treated with sPDT at the Department of Neurosurgery of the Military-Medical Academy S. M. Kirov, from 2020 to November 2021. Three patients were treated with sPDT again after 3, 7, and 15 months due to relapse.

Results: The median age of the patients was 55.5 years, range was 30–60 years, there were six men and four women. At the time of sPDT, 7 (70%) patients with recurrent tumors were diagnosed with glioblastomas (WHO grade IV), and 3 (30%) with anaplastic astrocytomas (WHO grade III). Tumors were without IDH mutation in 7 (70%) patients; MGMT gene expression status was evaluated in tumors in 9 (90%) patients. A 1p/19q co-deletion was not detected in any of the patients. The median tumor volume was 5.85 cm^3 (min. 3.2 cm^3, max. 22.5 cm^3). We have found that the median recurrence-free period after sPDT in patients with anaplastic astrocytomas and glioblastomas was 435 and 195 days, respectively.

Conclusion: This result allows to consider sPDT as one of the perspective methods of treatment of patients with recurrent gliomas of high malignancy in cases when repeated open surgical intervention has high risks of new neurological deficit.

Keywords: Photodynamic therapy, Fluorescence spectroscopy, Glioma, Glioblastoma; 5-aminolevulinic acid (5-ALA)

INTRODUCTION

Malignant gliomas remain a serious medical and social problem at present. Despite the combined standard and variety of experimental treatment options, the prognosis for gliomas of high malignancy remains poor. Glioblastoma is the most common glial tumor among neuroepithelial tumors and has the least favorable prognosis. It accounts for 45–50% of all gliomas, is the most frequent cause of death in central nervous system pathology, has the worst prognosis, and is considered extremely resistant to adjuvant treatment.[1] For patients with primary glioblastoma, the median survival rate is 13 months for total resection, 11 months for subtotal resection, and 8 months for partial resection.[2] Progression or relapse of the disease is almost inevitable and occurs on average in 40–50% of patients during the first year and in 73.5–89.4% of patients during the second year.[3] A common treatment strategy for patients with recurrent tumors has not yet been established, and often an individual approach to the choice of treatment tactics is used. The need for surgical intervention in relapsed tumors is debatable, and the efficacy of surgical treatment is controversial.[4–6] At the same time, there is evidence that surgical removal of recurrent tumors apparently contributes to an increase in overall survival.[7]

Unsatisfactory results of glial tumor therapy make it necessary to search for new treatment options, including surgical ones. One of these directions can be the use of various physical factors of influence on tumor cells. Tumor treatment based on the effects of various physical factors is widely used in modern oncology. They include laser interstitial thermal therapy,[8] cryodestruction,[9] and hyperthermic ablation,

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achieved by radiofrequency current,[10] and high-intensity focused ultrasound.[11] The compatibility of these physical methods of exposure with neuronavigation systems and their accessibility make these methods attractive for precise local destruction of tumor tissue and allow neurosurgeons to perform cytoreduction of gliomas with accurate guidance on anatomical structures with minimal risk of neurological complications.

One of the modern methods of treating oncological diseases of various localizations is photodynamic therapy (PDT).[12] PDT can be performed either during open operations on the brain, as an additional method after resection of the main tumor mass,[13] or as an additional selective illumination of a functionally important area of the brain, where further resection would lead to persistent neurological deficits. PDT can also be performed as an independent method of treatment during stereotactic surgeries for deep-seated brain tumors.[14] To date, literary data describing the technical nuances of this method are very scarce, and the effectiveness of PDT in stereotactic surgeries is represented by a single publication without a description of long-term follow-up.

OBJECTIVES

To evaluate the safety and efficacy of sPDT in patients with recurrent malignant supratentorial gliomas.

MATERIAL AND METHODS

We analyzed the data of 10 patients with recurrent malignant gliomas of the brain who were operated on at the Clinic of Neurosurgery of the Kirov Academy of Medical Science from 2020 to November 2021. Adjuvant therapy was performed at federal or regional medical institutions. Histological verification of tumors was performed according to the 2016 WHO Classification.[15] According to the consilium of clinic physicians, the use of sPDT was considered indicated when resection or other types of local stereotactic treatment were unsafe or the patient refused them with the right to new treatment options. All patients gave written informed consent for this type of surgical treatment.

Preoperative preparation

Four hours before PDT, an oral solution of 5-aminolevulinic acid (ALASENS (SSC NIOPIK) in a dosage of 20 mg/kg) was given, and then under local anesthesia, a frame of the stereotactic navigation system CRW Precision (Integra, USA) was fixed on the patient's head. All patients underwent preoperative stereotactic MRI of the brain with contrast enhancement. According to the results of stereotactic calculations, intervention trajectories and target points in the tumor were simulated on a stereotactic phantom using Integra Radionics software (USA).

Fluorescence spectroscopy

The surgical intervention was performed using combined anesthesia (local anesthesia with Ropivacaine 0.5% in 40 mL + intravenous administration of Dexdor solution 0.8–1.2 mcg/kg/h, followed by correction after saturation at 0.4–0.8 mcg/kg/h). In the operating room, the guiding device was oriented along the selected trajectory. According to the calculated trajectory, a Y-shaped fiber-optic probe of the spectrometer LESA-01 "Biospect" (Russia) was immersed into the brain in the direction of the target point. Fluorescence biospectroscopy was performed along each trajectory, step by step, as the probe dipped every centimeter. As we moved toward the target point, we recorded an increase in fluorescence intensity at a wavelength of 632.8 nm, corresponding to the emission maximum of protoporphyrin IX (PP IX). In the area of the highest fluorescence intensity of PP IX along the trajectory and at the target point of intervention, material was collected for histological analysis.

Photodynamic therapy

After reaching the target point, a light guide with a cylindrical diffuser at the end (diameter 1.8 mm, length 22 mm) was introduced into the biopsy cannula [Figure 1] and PDT was performed using a 635 nm diode laser with a 1 watt output for 15 minutes at each point using a LUXB machine (South Korea). In each case, the number of target sites for PDT was selected individually and calculated based on the MRI data of the brain with stereotactic markings performed on the day of surgery. Fluorescence biospectroscopy was performed after PDT along all trajectories in 1-cm increments. At the same time, there was a significant decrease in the fluorescence intensity of PP IX in the exposed areas. [Figure 2]. Verbal and visual control of the neurological status was performed during the operation [Figure 3].

Postoperative care

Postoperative MRI of the brain with contrast was performed 24–48 h after SFDT in all patients, and thereafter, a control MRI with intravenous contrast every 2–3 months. RANO criteria were used to determine the presence of continued growth.[16]

Statistical methods

Statistical data were analyzed using Statistica 10.0, MedCalc. The recurrence-free period and post-relapse overall life expectancy from the date of sPDT were used to objectively evaluate the efficacy of sPDT.

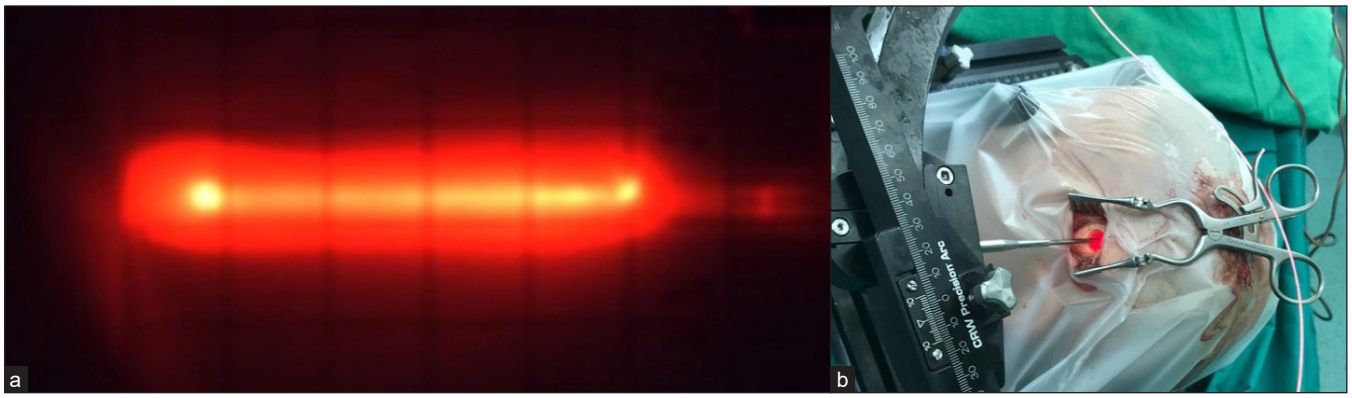

Figure 1: (a) Cylindrical diffuser with 635 nm laser light for PDT. (b) Intraoperative picture during sPDT. In the center is the operating field with the laser on.

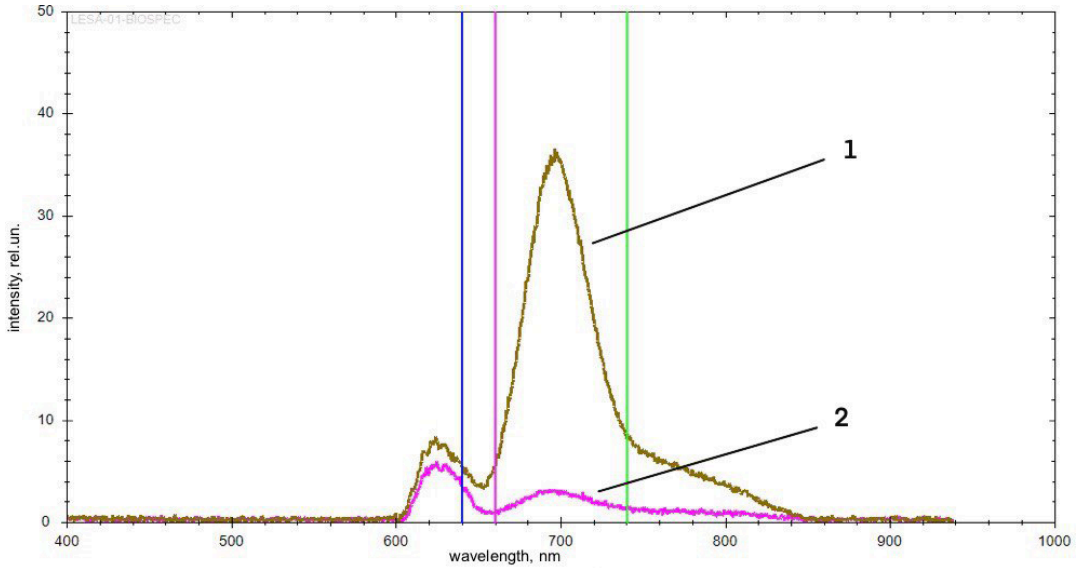

Figure 2: Fluorescence spectrum at the trajectory target: before (1) and after (2) PDT irradiation with 157 J/cm^2.

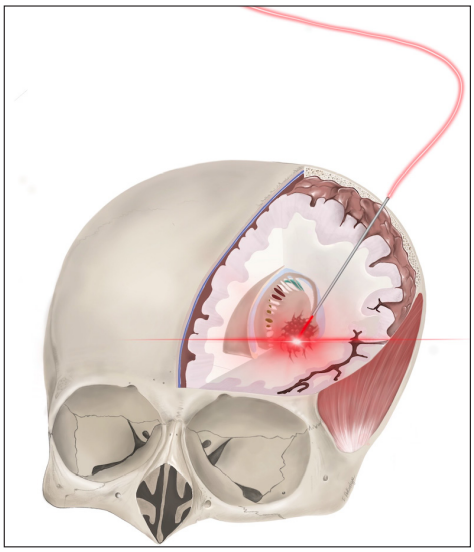

Figure 3: The technique of stereotactic photodynamic therapy.

RESULTS

Based on the data from literature sources[17] compared with the results of preoperative planning and postoperative MRI, the following indicators were determined: the phototoxic effect is achieved from the diffuser surface and to a depth of 4.5–6.5 mm (average is 5.5 mm), with the laser energy dose at this calculated depth averaging 157 ± 22 J/cm^2. Assessment of energy illumination was performed using the "Optical power meter QB230" (ADVANTEST Corp., Japan). According to the data of postoperative MRI study, we determined: approximate effect size with one diffuser was 3.4 × 1.3 × 1.3 cm, total volume from one diffuser averaged 2.75 ± 0.23 cm^3.

The study included 10 patients with a verified recurrence of high-grade gliomas in a functionally significant area who underwent sPDT. Three patients underwent repeated sPDT after 3, 7, and 15 months due to relapse.

At the time of sPDT, 7 (70%) patients with recurrent tumors were diagnosed with glioblastomas (WHO grade IV) and 3 (30%) had anaplastic astrocytomas (WHO grade III). In 2 (20%) patients, there was a malignant transformation of initially diagnosed WHO grade II diffuse astrocytoma during relapse into glioblastoma and anaplastic astrocytoma. In 7 (70%) patients, the IDH1 R132H mutation was not detected in the tumor, and 2 patients (20%) had the IDH1 R132H mutation. MGMT gene expression status was evaluated in tumors in 9 (90%) patients. In none of the patients was a combined 1p/19q deletion detected. Molecular genetic status analysis was not performed in one patient. The median age at the time of SFDT was 55.5 years (min. 30, max. 66). The median Karnofsky scale before and after surgery was 80 (max. 90, min. 70) and 80 (max. 90, min. 40), respectively [Table 1].

The median target tumor volume (volume of the contrastable part of the tumor) for SFDT was 5.85 cm^3 (range 3.2–22.5 cm^3), the average number of stereotactic trajectories was 4 (range 2–7). At least one irradiation session was performed in each target point along the trajectory, and when indicated (determination of residual level of PP IX after irradiation, in biospectroscopy) either a repeated irradiation session was performed in this target point, or with an offset from it along the same trajectory [Table 2].

Two patients developed motor aphasia and hemiparesis in the postoperative period. The neurological deficit was transient and regressed in the early postoperative period.

All patients treated with sPDT were referred to regional oncological institutions for further treatment. Chemotherapy with temozolomide was performed in 4 (40%) cases, irinotecan chemotherapy in combination with bevacizumab targeted therapy – in 6 (60%) cases, repeated radiotherapy with temozolomide combined administration was performed in 3 (30%) cases. Due to tumor progression after combined treatment (sPDT, chemotherapy), repeated sPDT was performed in 3 cases.

We found that the median recurrence-free period after sPDT in patients with anaplastic astrocytomas and glioblastomas was 435 and 195 days, respectively [Figure 4], As seen in Figure 3a, the 6-month survival rate after sPDT in patients with glioblastomas was 33.3%.

As seen in Figure 4, the 6- and 12-month survival rates after sPDT for patients with glioblastomas were 80.0% and 53.3%, respectively. The median post-relapse survival in patients with glioblastomas was 473 days (min. 14 – max. 602), whereas it was not reached in patients with anaplastic astrocytomas.

In the postoperative period, patients underwent brain MRI every 2–3 months after sPDT. Most patients had positive dynamics in the radiological picture: MR signs of a significant decrease in the volume of tumor tissue, reduction of contrast agent accumulation in the surgical intervention zone. In six cases, the recurrence reliably occurred not in the area of surgical intervention, but distantly, at an average distance of 4.8 mm [Figure 5]. Patients underwent PET/CT with [11C]-methionine to differentiate radiation necrosis from continued tumor growth [Figure 6].

Table 1: Patient characteristics.

Characteristics at the time of the sPDT	Number of patients (n = 10) (Number of SFDT cases n = 13)
Age (years)	
median	55.5
min, max	30, 60
Gender, n (%)	
male	6 (60%)
female	4 (40%)
Karnofsky Scale Index, n (%)	
>70	8 (80.0%)
<70	2 (20.0%)
Symptoms, n (%)	10 (100%)
seizures	6
Movement disorders	4
Verbal disorders	5
Side of the lesion, n (%)	
Right	3 (30%)
Left	7 (70%)
Localization, n (%)	
Depthly located	1 (10%)
Functionally significant areas	9 (90%)
Grade (during a recurrence)	
IV	7
III	3
Grade (at the time of the initial diagnosis)	
IV	4
III	4
II	2
No genetic testing, n	1
MGMT expression, n	
low/medium	9
high	-
IDH1/IDH2 mutation, n	
wilt-type	7
with	2
1p/19q, n	
absent	9
present	0

DISCUSSION

Currently, maximally radical and safe microsurgical resection is the standard of treatment for gliomas treatment. Total resection of a primary malignant glioma leads to a

Table 2: Characteristics of the treatment.

Methods of treatment	**Number of cases (n = 10)**
Treatment before sPDT, n (%)	10
Open tumor resection	7 (70.0%)
Stereotactic cryodestruction	3 (30.0%)
Chemo-radiation therapy	10
Chemotherapy	10
Characteristics of sPDT	
Target tumor volume	
median(cm^3)	5.85
min-max	3.2–22.5
Number of trajectories	
Medium, n	4
min-max	2–7
Treatment after sPDT	
Radiation therapy, n (%)	3 (30.0%)
Chemotherapy, n (%)	4 (40.0%)
Targeted therapy, n (%)	6 (60.0%)
Repeated sPDT, n (%)	3 (30.0%)

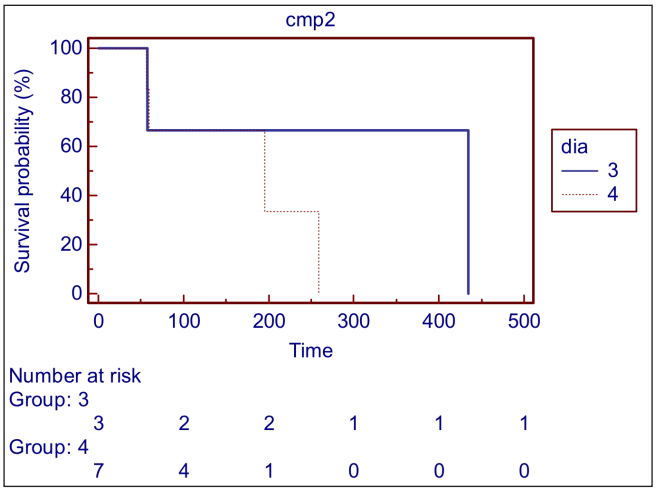

Figure 4a: Kaplan–Meier curve. Recurrence-free period after sPDT for patients with anaplastic astrocytomas (3), for patients with glioblastomas (4).

longer overall life expectancy compared with partial tumor resection and biopsy, and is independent of IDH-mutation status and O6-methylguanine-DNA-methyltransferase promoter methylation.[18] The data on the role of surgical resection in the treatment of recurrent malignant gliomas are controversial.[19] Many patients with recurrent glioblastoma receive only conservative treatment, with a median life expectancy of 7–10 months.[20,21] Only about 20–30% of patients with glioblastomas are candidates for resection of a recurrent tumor,[22] considering the localization and volume of the tumor that can be safely resected.[21]

Tumor location in functionally significant and deep areas of the brain are important risk factors for surgery-related complications and a major cause of incomplete glioma resection.[23,24] Surgical treatment using minimally invasive cytoreduction techniques has shown that these methods are safe and effective in patients with small supratentorial gliomas of any localization, and in

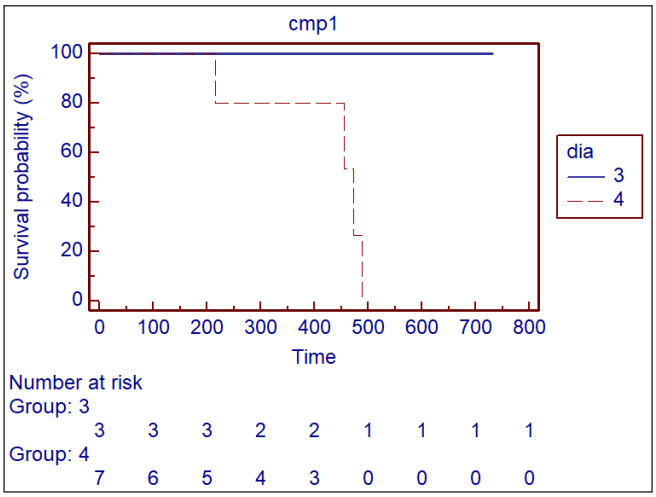

Figure 4b: Kaplan–Meier curve. Total life expectancy after sPDT for patients with anaplastic astrocytomas (3), for patients with glioblastomas (4).

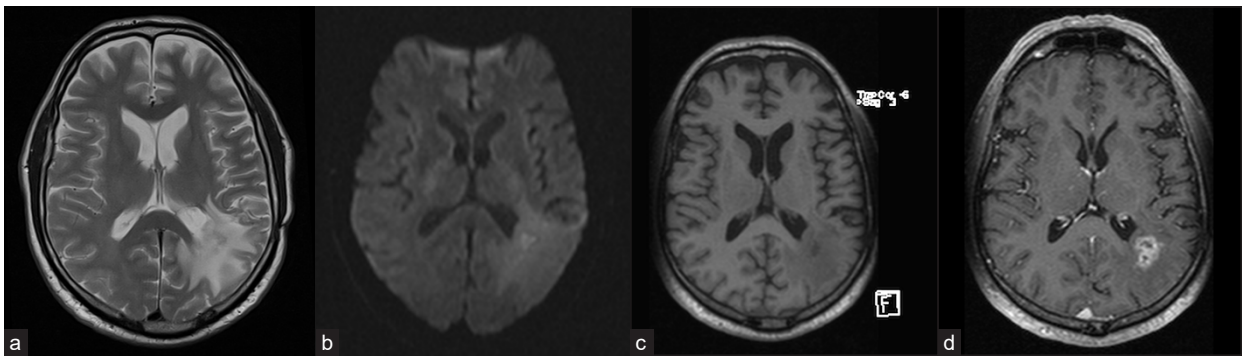

Figure 5.1: Contrast-enhanced MRI of the brain before sPDT: (a) T2; (b) DWI (b 1,000); (c) T1, before contrast; and (d) post-contrast T1.

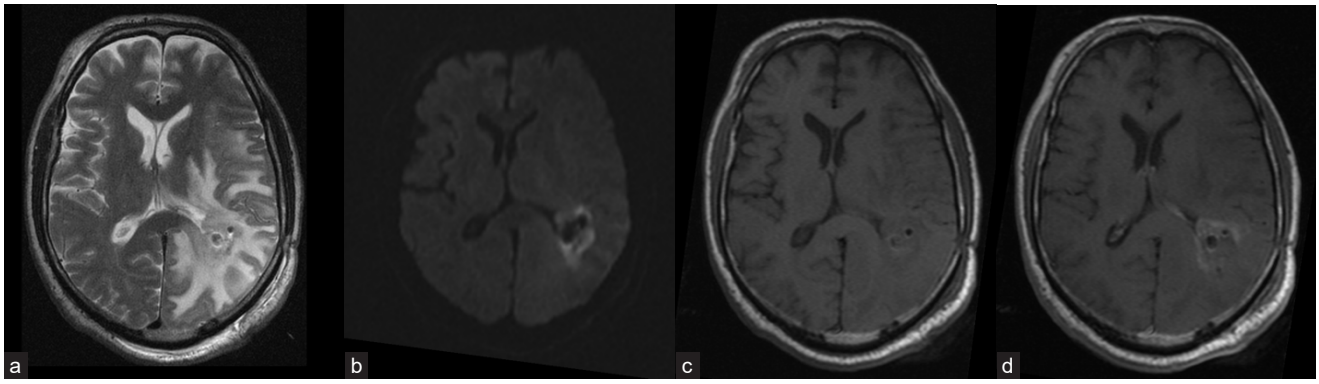

Figure 5.2: Contrast-enhanced MRI of the brain after sPDT: (a) T2-increase of perifocal edema area; (b) DWI (b 1,000) – diffusion restriction in the intervention area; (c) T1, before contrast - slight increase of signal intensity in the intervention area; and (d) post-contrast T1 – decrease of contrast agent accumulation in the intervention area.

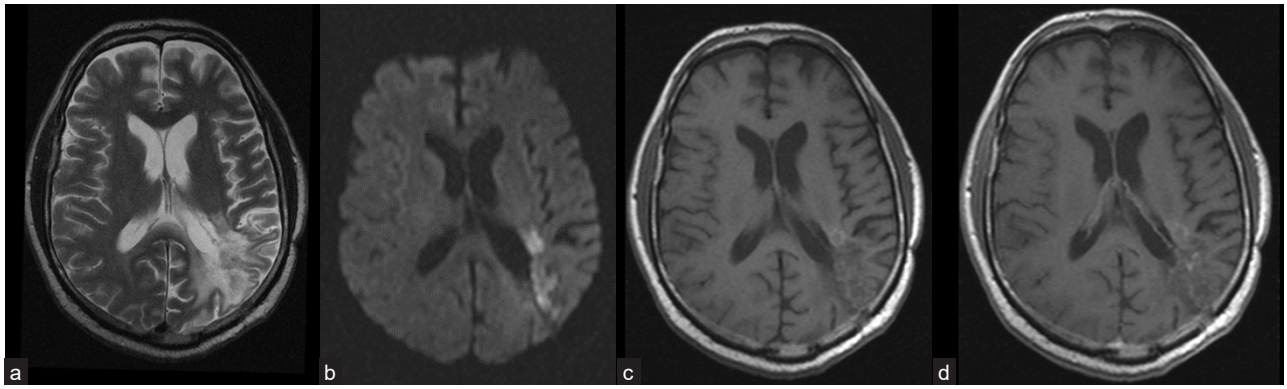

Figure 5.3: Contrast-enhanced MRI of the brain 6 months after sPDT: (a) T2- reduction of perifocal edema area; (b) DWI (b 1,000) – restriction of diffusion in and to the treatment zone; (c) T1- before contrast – small hyperintense area to the front of the treatment zone; and (d) post-contrast T1 – small area of slight contrast substance accumulation in the treatment zone.

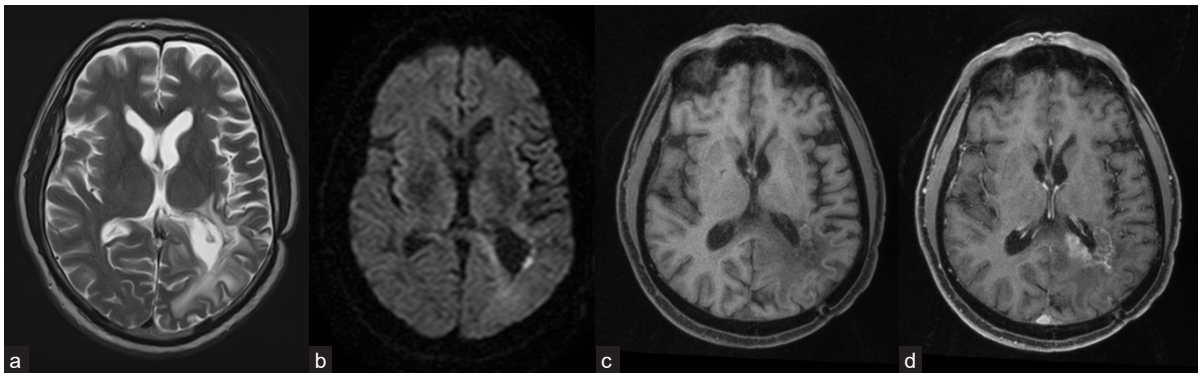

Figure 5.4: Contrast-enhanced MRI of the brain 14 months after sPDT (recurrence): (a) T2; (b) DWI (b 1000) – small area of diffusion restriction in the exposure area persists; (c) T1, before contrast; and (d) post-contrast T1 – small area of contrast substance accumulation and appearance of a new area of contrast substance accumulation with sizes 38 × 36 × 33 mm.

combination with microsurgical removal in patients with extensive hemispheric gliomas spreading to functionally significant and deep areas of the brain.[9,25–27]

The use of PDT in the treatment of malignant gliomas has increased over the past decade in both open and stereotactic interventions for primary and recurrent tumors.[14,28–31] Our research presents the experience of treating 10 patients with recurrent malignant gliomas located in deep or functionally significant brain structures using sPDT, with patients without the IDH1/2 mutation predominating among them (7 of

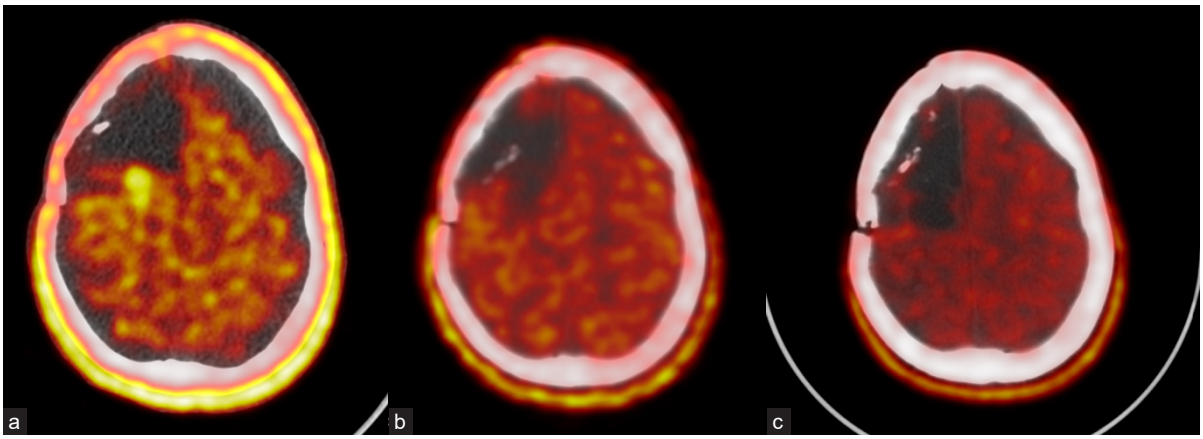

Figure 6: PET/CT with [11C] methionine (a) on the posterior border of the postoperative cyst a zone of increased accumulation = 2.4, size 13 × 24 × 17 mm; (b) 1 month after PDT; and (c) 9 months after PDT – no recurrence.

Table 3: Analysis of other studies.

Author	Patient count	PDT for	Tumor volume	Grade	The effect of PDT
Tobias J. Beck, Friedrich W. Kreth (2007)[17]	10	recurrence	5.9 cm^3 (2.1–10.2 cm^3)	III—IV	Median post-relapse survival 15 months.
Ann Johansson, Florian Faber (2013)[37]	5	Recurrence	5.92 cm^3 (1.5–10.0 cm^3)	IV	Median post-relapse survival 15 months.
Stefanie Lietke, Michael Schmutzer (2021)[29]	44	Recurrence	3.34 cm^3 (0.5–22.8 cm^3)	III—IV	Median post-relapse survival 13 months.
Our data	10 patients (count of PDT is 13)	Recurrence	5.85 cm^3 (3.2–22.5 cm^3)	III—IV	Median post-relapse surviva: -Gr IV 15.8 mos., y G III not achieved.

9 examined). The average follow-up time after sPDT was 12 months (2.4–24.4 months).

Our experience showed that the median recurrence-free period after sPDT in patients with recurrent anaplastic astrocytomas and glioblastomas was 14.5 and 6.5 months, respectively, and the median post-relapse overall life expectancy in patients with recurrent glioblastomas was – 15.8 months. These data are comparable with the results of interstitial PDT using 5-ALA in patients with recurrent malignant gliomas presented in a retrospective study performed at the University Hospital of Munich.[29] The median recurrence-free period after interstitial PDT in this study was 6.8 months and the median post-relapse overall life expectancy was 12.5 months, and patients were grouped into a single group of malignant gliomas without specification of the histological type of recurrent tumor. The latter does not allow us to fully assess the effectiveness of this method in patients with recurrent gliomas of different histological types. In patients who underwent microsurgical resection of a recurrent tumor post-relapse overall life expectancy ranges from 5 to 13 months, with the maximum increase achieved only with total removal of the contrasting part of the recurrent glioblastoma.[25,32–34] A similar increase in life expectancy from 9.0 to 11.2 months after laser interstitial thermotherapy has been demonstrated in several studies in patients with recurrent glioblastoma [Table 3].[35–37]

At the same time, with repeated irradiation or stereotactic radiosurgery, the median post-irradiation life expectancy in patients with relapsed unresectable glioblastoma was about 9 months, which is significantly lower than the figure achieved in our study.[38]

Therefore, sPDT – the safest possible cytoreduction of recurrent malignant gliomas that are refractory to other therapies and cannot undergo microsurgical resection, increases post-recurrence life expectancy, especially in patients with glioblastomas without an IDH mutation.

CONCLUSION

As far as we know, this is the first study in our country analyzing the results of the treatment of patients with recurrent malignant gliomas using sPDT with 5-ALA. The obtained result allows us to consider sPDT as one of the perspective methods of treatment for patients with recurrent high malignant gliomas in cases where repeated open surgical intervention has high risks of neurological deficit development. There are still unresolved questions about

the technique of sPDT, minimum sufficient, and maximum allowable doses of energy to achieve a positive result. Further clinical and experimental interdisciplinary research is required to reliably assess the effectiveness of sPDT in treating gliomas of high malignancy.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Competing interests

No funds, grants, or other support was received. The authors have no competing interests to declare that are relevant to the content of this article.

Consent to publish

Participants have consented to submit their medical histories to the journal. Patients signed informed consent regarding the publication of their data and photographs.

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