PHOTODYNAMIC THERAPY IN NEUROONCOLOGY

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Abstract

Literature review reflects the current status and development status of intraoperative photodynamic therapy in neurooncology and discusses the results of the most important studies on photodynamic therapy (PDT). We searched the Pubmed, EMBASE, Cochrane Library and eLibrary databases for publications published between January 2000 and December 2022. Found 204 publications in foreign sources and 59 publications in domestic editions, dealing with the issues of photodynamic therapy in neurooncology. An analysis of the literature has shown that intraoperative PDT in neurooncology is an important tool that contributes to increasing the radicality of the operation and local control. The basic rationale for the effectiveness of PDT lies in the study of the pathways leading to the complete devitalization of a malignant tumor, the study of the mechanisms of the local and systemic immune response. In addition, subcellular targets in PDT are determined by the properties of photosensitizers (PS). Second generation PSs have already been introduced into clinical practice. The effectiveness of PDT using photoditazine, 5-aminolevulinic acid has been demonstrated. The mechanisms of action and targets of these PS have been established. In Russia, a number of studies have repeatedly shown and proved the clinical effectiveness of PDT in groups of neurooncological patients with glial tumors and secondary metastatic tumors, but so far, the method has not been included in the clinical guidelines for the provision of high-tech neurosurgical care. There is certainly a need for further development of PTD techniques in neurooncology, especially in patients at high risk of recurrence and aggressive CNS tumors.

Key words: photodynamic therapy, photosensitizer, photoditazine, 5-ALA, neurooncology, apoptosis, necrosis, meningioma, recurrence, glioblastoma, metastasis.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В НЕЙРООНКОЛОГИИ

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Резюме

Выполнен обзор литературы, отражающий современное состояние и степень разработанности методики интраоперационной фотодинамической терапии (ФДТ) в нейроонкологи. Представлены к обсуждению результаты наиболее значимых исследований, посвященных ФДТ в нейроонкологии. Проведен анализ научных публикаций по данной тематике в базах данных Pubmed, EMBASE, Cochrane Library и eLibrary, опубликованных в промежуток времени с января 2000 г. по декабрь 2022 г. Найдено 204 публикации в зарубежных источниках и 59 публикаций в отечественных изданиях, в которых рассматриваются вопросы применения ФДТ в нейроонкологии. Анализ литературы показал, что в клинической практике интраоперационная ФДТ в нейроонкологии является важным инструментом, способствующим увеличению радикальности операции и локального контроля. Фундаментальное обоснование эффективности ФДТ заключается в изучении путей, ведущих к полной девитализации злокачественной опухоли, изучении механизмов локального

и системного иммунного ответа. При этом субклеточные мишени при ФДТ обусловлены свойствами фотосенсибилизаторов (ФС). В многочисленных исследованиях показана противоопухолевая эффективность использования ФДТ с ФС на основе хлорина е6, 5-аминолевулиновой кислоты, производных порфиринов. Установлены механизмы действия и мишени этих ФС. В России в ряде исследований подтверждена клиническая эффективность ФДТ у групп нейроонкологических пациентов с глиальным опухолями и вторичными метастатическими опухолями, однако до сих пор метод не включён в клинические рекомендации по оказанию высокотехнологичной нейрохирургической помощи. Безусловно, необходима дальнейшая разработка методики ФДТ в нейроонкологии, особенно у пациентов с высоким риском рецидива и агрессивными опухолями ЦНС.

Ключевые слова: фотодинамическая терапия, фотосенсибилизатор, фотодитазин, 5-аминолевулиновая кислота, нейроонкология, менингиома, глиобластома, метастазы, рецидив, апоптоз, некроз.

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Introduction

One of the most challenging tasks in oncology is the treatment of malignant tumors of the central nervous system (CNS). The average life expectancy of such patients after surgery, even with adjuvant therapy, is, on average, 14 months for glioblastoma multiforme and 25 months for anaplastic astrocytoma. Despite the successes of recent decades in understanding the fundamental principles of the mechanisms of neurooncogenesis, over the past 30 years the average life expectancy of patients has increased by only 2–4 months [1-3]. That is why it is necessary to develop alternative methods of treating neuro-oncology patients.

The study and development of photodynamic therapy (PDT) techniques for the treatment of malignant brain tumors in the Russian Federation began at the Russian Neurosurgical Research Institute (RNSI) named after. prof. A.L. Polenov back in 2001, where the foundations were laid and the first patents were obtained, and a protocol for the use of PDT in patients with glial tumors was developed [4, 5].

Outside the Russian Federation, research on the use of PDT in neuro-oncology began back in the 1990s [6]. However, at the moment, in many countries, the use of PDT for the treatment of malignant brain tumors remains within the framework of research activities. An exception is Japan, where since September 2013, PDT has been approved as a new and effective technique for increasing the degree of radicalization of surgical treatment of malignant glial tumors and has been included in the standards of medical care [7]. There are also literature data on the effectiveness of intraoperative PDT in the treatment of malignant meningiomas (median survival is reported to reach 23 months), however, reports are rare and patient groups are small [8].

In our opinion, at the present stage of development of the subject and further progress in PDT technology in neuro-oncology, the relevant directions are: minimizing the effect on healthy tissue, developing new generations of photosensitizers (PS), optimizing routes for delivering PS to target points, and developing new fiber-optic technologies. The main goal of this work is to present the current state and degree of development of intraoperative PDT in neuro-oncology based on the analysis of domestic and foreign literature, and to discuss the results of the most significant studies on PDT. The review examines the principles, advantages and disadvantages of PDT in the structure of complex treatment of malignant brain tumors, types of PS and methods of its delivery to the central nervous system, modern fiber-optic technologies in PDT, and demonstrates possible directions for further development of PDT technology in neuro-oncology.

The search of the studies published from January 2000 to December 2022 was performed in the Pubmed, EMBASE, Cochrane Library and eLibrary databases, using the query “photodynamic*[ti] AND therapy*[ti] AND (brain tumor* [ti] OR gliom*[ti] OR glioblastoma*[ti] OR meningiom*[ti] OR brain metast*[ti])” for foreign works and the keywords “photodynamic therapy AND (glioblastoma* OR gliomas* OR meningiomas* OR brain OR intracerebral metastases*)” for domestic ones. During the search, duplicate articles in different databases have been excluded, only peer-reviewed publications, excluding abstracts and publications based on conference proceedings, have been included.

204 publications were found in the Pubmed, EMBASE, and Cohrane Library databases, of which 26 were review articles, and only 2 systematic reviews that met the requirements of the international PRISMA system. In the eLibrary database, issues of PDT in neuro-oncology are discussed in 59 publications. This work analyzes literature data from both foreign and domestic authors.

Photosensitizers

Photosensitizers (PS) are one of the three main components of PDT. Properly selected PSs must meet a number of requirements, including the absence of systemic toxicity, selective accumulation in tumor tissue and acti-

vation at light wavelengths sufficient for deep penetration into brain tissue, minimal exposure to surrounding brain tissue, ease of administration of the drug into the patient's body, and clear visible fluorescence when visually assessing the degree of PS accumulation [9].

According to the publications, there are three generations of photosensitizing compounds [10, 11]. The molecules of the first generation of PS (photofrin, temoporfin, verteporfin) consist of naturally formed porphyrins, including hematoporphyrin (HpD). These compounds are activated at wavelengths of about 400 nm [12]. First generation PS drugs have a number of significant disadvantages: first, they have a low quantum yield of singlet oxygen, and as a result, lower efficiency; second, they realize their effect at wavelengths close in spectrum to natural light, having a pronounced phototoxic effect on the skin. First-generation PSs have a longer half-life of the drug compared to next-generation PSs [13].

In neuro-oncology, second-generation PSs are most often used, such as chlorins (photoditazin, photoran) and aminolevulinic acid derivatives (alasens). These drugs are activated by wavelengths of more than 600 nm and are most effective in generating singlet oxygen species [14, 15]. Recently, borated derivatives of porphyrins and chlorins have been actively studied in connection with the prospect of their use in PDT. The ability of borated derivatives of chlorin e6 and porphyrin (which are mono-, di- or tetraanions) to penetrate flat bilayer lipid membranes has been studied [16]. The advantage of these drugs is the accumulation of PS mainly in the mitochondria of tumor cells, which requires less light energy and minimizes side effects to almost zero. However, these drugs are more expensive and are yet used in experiments [15-17].

Today, active development of the third generation FS is underway. There are three main groups of third-generation PSs, namely, nanotechnological (nanoparticles, mesoporous structures, etc.), genetically engineered and carrier-conjugated (antibodies against tumor antigens, liposomes, vesicles). A number of studies have shown that third-generation PSs conjugated to specific carriers are characterized by the most pronounced specificity and tropism for malignant tumor tissues. For example, neuropilin-1 (receptor for endothelial growth factor) is overexpressed in glioblastoma and is involved in tumor neoangiogenesis. Conjugation of PSs with an antibody to neuropilin-1 provides a targeted effect on the tumor and also reduces blood flow in the tumor by approximately 50% [18].

Conjugation of PSs with an antibody to neuropilin-1 can increase the uptake of PS by tumor cells. In 2020, A. K. Rajora's et al. used apolipoprotein E3 nanoparticles (the E3 chaperone for cholesterol transit in the brain communicates with low-density lipoprotein receptors in glioblastoma cells) to facilitate the delivery of PS to tumor tissue [19].

M.A. Shevtsov et al. (2022) demonstrated that the membrane-bound protein mHsp70 is present in glioblastoma tumor cells but not in healthy cells. The authors have developed a drug based on an antibody to mHsp70 – the RAS70 peptide conjugated with PS, which will allow it to be used in the future for intraoperative fluorescence diagnostics, and possibly for PDT [20, 21].

Methods for delivering photosensitizers to the brain

The optimal method of drug delivery should be safe, minimally invasive, easy to learn and use. The main and alternative routes of drug delivery to the brain currently used are direct introduction of the active substance into tumor tissue, installation of an implantable pump system, use of devices for drug delivery with temporary disruption of the integrity of the blood-brain barrier (BBB), as well as transnasal, intravenous and oral administration of drugs [18, 22]. The intravenous route of administration has a number of obvious advantages, but faces the problem of molecules of active substances crossing the BBB [18]. Recent scientific advances offer opportunities to overcome such limitations with varying degrees of effectiveness. One of the possible solutions to this issue seems to be the use of phonophoresis. Ultrasound has demonstrated the potential to deliver drugs non-invasively across the BBB precisely to the desired area [22]. The use of targeted nanoparticles makes it possible to create the required drug concentration and reduce delivery time by improving the solubility and bioavailability of hydrophobic drugs [23].

In addition to the BBB, an obstacle to the delivery of drugs to the tumor is its heterogeneous and dynamically changing microenvironment. It is known that the microvasculature in glial tumors has a permeability of 7 to 100 nm, which is significantly less than that of tumors of other localizations (380-780 nm). To solve this problem, scientists propose using viruses that act as vectors that deliver the agent of interest [24]. Recently, in molecular medicine there has been increased interest in the use of quantum dots (nanomaterial with specific spectral characteristics), which have unique optical properties that provide high sensitivity and selectivity [25]. Another possible promising solution may be the use of magnetic nanoparticles [26]. Gold nanoparticles coated with covalent glycans, complementary to the cerebral vascular endothelium, have shown great potential for the delivery of therapeutic agents to the central nervous system [27, 28].

Fiber-Optic Technologies

When performing PDT, light of a certain wavelength and high intensity is required. Absorption of light quanta by PS molecules in the presence of oxygen leads to photochemical reactions (reactions of types I and II). Figure 1 shows a diagram of the reactions that occur during PDT.

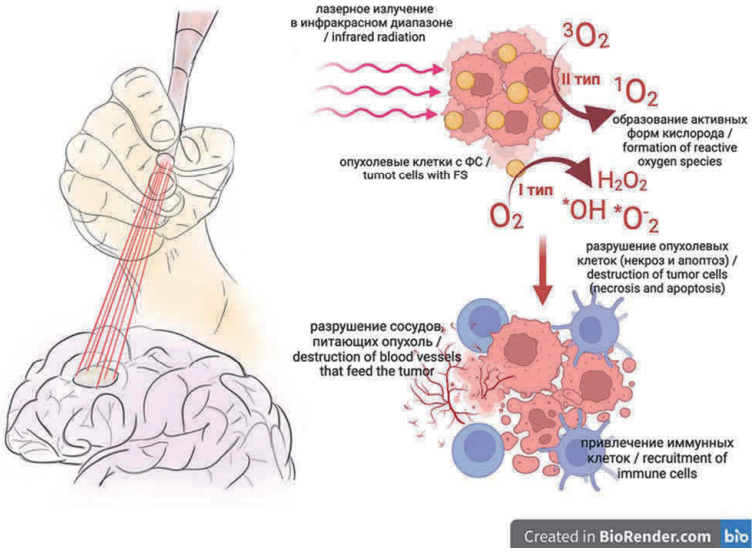

Рис. 1. Схематическое изображение реакций, происходящих при проведении фотодинамической терапии (ФС – фотосенсибилизатор).
Fig. 1. Scheme of the course of the reaction in photodynamic therapy (PS – photosensitizer).

Shown schematically in Fig. 1 singlet forms of oxygen cause cell death through the mechanisms of necrosis and apoptosis [29-32]. Both types of reactions occur simultaneously, and their effect ratio depends on the oxygen concentration in tissues, the pH of the environment and the composition of the substances used [33]. Carrying out PDT on the bed of a removed tumor increases the radicality of the operation, since the depth of light penetration, according to various studies, ranges from 5 to 12 mm [34-36]. The effectiveness of PDT, as well as its cytotoxicity, is influenced by many factors, including the type of PS, the administered dose of PS and light dose, as well as the presence of oxygen and the time interval between the administration of PS and exposure to light [37, 38]. It is known that tumor cells are often "hypoxic", and the main metabolic pathway is anaerobic glycolysis, which is problematic since PDT requires triplet O_2 in the ground state. In order to solve this problem at A.L. Polenov RNSI proposed creating controlled hyperoxia by increasing the partial pressure of oxygen in the oxygen-air mixture to 60%, which increases the formation of singlet oxygen (patent No. 2318542 dated March 10, 2008) [5].

In the work of D. Bartusik-Aebisher et al. (2022) the authors proposed a singlet oxygen generator based on the fiber-optic method for its targeted delivery during PDT. The goal of the idea is to develop a heterogeneous device for PDT that uses optical excitation of PS molecules released from the porous ends of a hollow microstructured optical fiber through which O_2 is supplied [39]. The essence of the work is to develop a methodology for bonding porous silicon to a commercially available hollow microstructured optical fiber, optimizing the optical coupling between the fiber and the bound PS, maintaining porosity throughout the bound silicon, and releasing the PS from the silicon matrix by irradiation with visible light.

The modern principle of PDT is the use of a single source of laser radiation, which is simultaneously used for photodiagnosis and PDT (the principle of phototheranostics), thereby ensuring spectroscopic monitoring of changes in the fluorescence intensity of the PS during laser irradiation. This achieves real-time PDT dose control, which leads to a therapeutic dose of light in the desired area and reduces photocytotoxicity to healthy tissues [40].

Clinical effectiveness

Many studies have shown the clinical effectiveness of surgical tumor resection in combination with PDT [41]. The article by W. Stummer et al. (2008) described a case of treatment of a patient with glioblastoma multiforme of the left frontal lobe who underwent surgical treatment with radiotherapy and chemotherapy. Twelve months after tumor resection, tumor recurrence was detected, and PDT was performed during re-resection. After oral administration of 5-ALA at a dosage of 20 mg/kg, irradiation was performed using a diode laser with a wavelength of 633 nm (with a power of 200 mW/cm^2) in continuous mode (light dose was 1200 J/cm^2). Subsequently, the patient lived for 5 years without tumor recurrence [42, 43]. C. Schwartz et al. (2015) in their study described a group of 15 patients who underwent PDT with 5-ALA at a dose of 20 or 30 mg/kg. Irradiation was carried out with a diode laser with a wavelength of 633 nm, the average light dose was 12.960 J. Patient survival was compared with the survival of patients who underwent only surgical resection of the tumor. Patients who underwent PDT showed a longer median disease-free survival, which reached 16 months, while in the second group this indicator was 10.2 months ($p < 0.001$). In 6 patients in the PDT group, the duration of recurrence-free survival was more than 30 months.

Seven out of fifteen patients were diagnosed with complications in the postoperative period, namely, transient aphasia and pulmonary embolism [44].

In the study by A.Yu. Ryndy et al. (2023) included 161 patients with a malignant glial tumor of supratentorial localization, of which 80 patients underwent PDT using photoditazine (1 mg/kg). The drug was administered intravenously during the induction of anesthesia. To irradiate the removed tumor bed, a Latus laser unit (ATKUS LLC, St. Petersburg) with a power of 2.5 W and a wavelength of 662 nm was used. Irradiation was carried out in a continuous mode, the duration of therapy depended on the area of the bed at the rate of a therapeutic light dose of 180 J/cm^2. The authors of the work proved that PDT as part of complex therapy for malignant gliomas of the brain significantly increases the median overall survival in patients with grade 4 gliomas – up to 20.7 ± 4.7 months (comparison group – 13.5 ± 2.3 months; p =0.0002); and also increases the median life expectancy without recurrence for patients with grade 3 gliomas – up to 21.7 ± 3.4 months (main group – 15.8 ± 3.1 months; p = 0.0002), and with grade 4 gliomas – up to 11.1±2.1 months (comparison group – 8.0±2.3 months; p=0.0001) [45].

The team at the Royal Melbourne Hospital has the largest clinical experience in the use of PDT in neuro-oncology, having studied more than 350 patients with gliomas. The authors used hematoporphyrin derivatives as PS at a dosage of 5 mg/kg (intravenous administration). The light dose ranged from 70 to 240 J/cm^2. In patients whose treatment regimen included PDT, 2-year survival rates for newly diagnosed and recurrent gliomas were 28% and 40%, respectively, and 5-year survival rates were 22% and 34%, respectively [46]. Regarding the side effects of PDT, as reported by S. Eljamel (2010), out of 150 patients who underwent PDT using 5-ALA and Photofrin, complications were identified in 7 patients: 3 (2%) patients developed deep vein thrombosis during treatment with Photofrin, none with 5-ALA-mediated PDT; 2 (1.3%) patients developed skin photosensitivity due to poor light protection in the summer months (0.6% with Photofrin-mediated PDT). After PDT, 2 (1.3%) patients developed cerebral edema requiring treatment, and one (0.1%) patient developed skin necrosis and wound liquorrhea from a previously irradiated skin flap [47]. Additional information about the use of various PSs and the clinical effectiveness of PDT in neuro-oncology is presented in Table.

Таблица
Сводные сведения о клинической эффективности ФТД в нейроонкологии
Table
Summary of clinical effectiveness of FTD in neurooncology

Автор, год Authors, publication year	Число пациентов Number of patients (n)	ФС, дозировка (мг/кг) PS, dose (mg/kg)	Доза света, (Дж/см^2) Light dose, (J/cm^2)	Нежелательные реакции при и после ФДТ (да/нет) Undesirable reactions during and after PDT (yes/no)	Медиана общей выживаемости (мес) Overall survival median, (months)
Хлорины Chlorins					
S. Stylli, 2005 [48]	78	Фотофрин I 5 мг/кг Photofrin I 5 mg/kg	70–240	Нет No	14,3
H. Kostron, 2006 [49]	26	Фоскан 0,15 мг/кг Foscan 0,15 mg/kg	20	Нет No	8,5
P.J. Muller, 2006 [50]	43	Фотофрин II 2 мг/кг Photofrin II 2 mg/kg	120	Нет No	11
Y. Muragaki, 2013 [51]	13	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	24,8
J. Akimoto, 2019 [52]	74	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	25

А.Ю. Рында, 2023 [45]	80	Фотодитазин 1 мг/кг Fotoditazin 1 mg/kg	180	Нет No	29,9
K. Shimizu, 2018 [53]	17	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	Не указана No data
M. Nitta, 2018 [54]	30	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	17,5
Tatsuya Kobayashi, 2022 [55]	70	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	16,0
C.W Teng, 2020 [56]	78 (крысы)	Нанокластеры цианина и хлорина 1 мг/кг Cyanine and chlorin nanocluster 1 mg/kg	30	Нет No	14,3
T. Maruyama, 2016 [57]	27	Талапорфин натрия 40 мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	24,8
E.I. Kozlikina, 2020 [58]	1	Талапорфин натрия 40, мг/м^2 Talaporfin sodium 40 mg/m^2	27	Нет No	14,5
A. H. Sara, 2015 [59]	30	Фотолон 4 мг/кг Fotolon 4 mg/kg	30	Нет No	15,0
J. Akimoto, 2016 [60]	27	Талапорфин натрия 2 мг/кг Talaporfin sodium 2 mg/kg	27	Нет No	24,8
		Порфирины Porphyrins			
W. Stummer, 2006 [61]	122	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	100	Нет No	15,2
S. W. Cramer, 2020 [62]	350	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	80-120	Нет No	16,1
S. Schipmann, 2020 [63]	30	5-АЛК, 20 мг/кг 5-ALA, 20 mg/kg	100	Нет No	12,1
W. Stummer, 2008 [64]	1	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	100	Нет No	56
C. Schwartz, 2015 [65]	15	5-АЛК 30 мг/кг 5-ALA 30 mg/kg	12,9	Нет No	32,4
K. Mahmoudi, 2019 [66]	10	5-АЛК 20 мг/кг 5-ALA 20 mg/kg	80	Нет No	18,9

ФС – фотосенсибилизатор; ФДТ – фотодинамическая терапия; 5-АЛК – 5-аминолевулиновая кислота.
PS – photosensitizer; PDT – photodynamic therapy; 5-ALA – 5-aminolevulinic acid.

Discussion

In neuro-oncology, the high rate of recurrence of malignant tumors is due to both the invasive type of tumor growth and its cellular resistance to traditional methods of adjuvant therapy [67, 68]. The cascade mechanisms that arise as a result of PDT cause alteration of cell membranes and lead to irreversible damage and destruction of photosensitized tumor cells. PDT not only directly affects tumor cells, but also reduces the vascularization (blood supply) of the tumor, causing an inflammatory response that stimulates a local and even systemic immune response. PDT does not affect the extracellular matrix, therefore, the tissue healing process is associated with a minimal risk of scar formation and adhesions, and the risk of infectious complications is reduced [66]. PDT is the subject of intensive research, although it has not yet become widespread in neuro-oncology, and only a few laboratories in the Russian Federation have transitioned it to clinical use [69–76].

PDT has been successfully used for more than two decades, however, in our opinion, the following problems still remain unresolved:

- Further development of PSs with greater selectivity of accumulation in tumor cells and tissues is necessary;
- Problem of skin photosensitivity;
- Problem of hypoxicity of malignant tumors;

There are certainly a number of advantages that determine the relevance and provide incentive for the further development of PDT technology:

- Low concentration of "free" PS in the body and rapid elimination;
- Impact on tumor cells adjacent to vital functional areas of the brain that are inaccessible to surgery;
- Ability to adapt existing endoscopic and microoptical techniques with new fiber optic equipment.

The prospect for further development of the topic of PDT in neuro-oncology is the development of a hybrid fiber-optic software and hardware complex based on technologies used in various fields of modern science: organic synthesis, physics, photochemistry, nanotechnology and artificial intelligence.

Conclusion

Due to the high selectivity of action, PDT therapy is a very promising technique compared to classical treatment methods used in neuro-oncology. Despite sample size limitations and the small number of randomized controlled trials, available evidence suggests a positive effect of PDT on the survival of patients with glioblastoma compared with standard therapy.

The main advantage of the PDT method is its high efficiency and minimally invasive nature. The high selectivity of the effect on brain tumor cells during PDT, the possibility of spectroscopic control and objectification of the dynamics of PS accumulation during irradiation allows to speak of PDT as an effective method for local control of neoplastic processes in the brain, which in turn leads to a long recurrence-free period and improvement quality of life of neuro-oncological patients. This approach in modern neuro-oncology can be considered as an option of theranostics and has the right to be called "photodynamic theranostics".

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