POSSIBILITIES OF INTERSTITIAL PHOTODYNAMIC THERAPY IN THE TREATMENT OF BRAIN GLIOBLASTOMA

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Abstract

Interstitial photodynamic therapy (iPDT) is a minimally invasive treatment method based on the interaction of light, a photosensitizer (PS) and oxygen. In brain gliomas, iPDT involves the stereotactic introduction of one or more light guides into the target area to irradiate tumor cells and tissues that have accumulated PS, which subsequently causes necrosis and/or apoptosis of tumor cells, destruction of the tumor vascular network and causes an inflammatory reaction that triggers stimulation of the antitumor immune response.

The aim of the study was to analyze the possibility of using iPDT in the treatment of unifocal, small-sized (up to 3.5 cm) glioblastomas.

The study with iPDT included 7 patients with a unifocal variant of glioblastoma with a maximum tumor size of up to 3.5 cm and a Karnofsky score of at least 70 points. In 5 patients (71.4%) there was a relapse of glioblastoma, in 2 cases (28.6%) the tumor was diagnosed for the first time. As a PS, PS photoditazine was used, administered intravenously by drip at a dose of 1 mg/kg. Interstitial irradiation was performed using a laser (Latus 2.5 (Atkus, Russia)) with a wavelength of 662 nm and a maximum power of 2.5 W and cylindrical scattering fibers. The target tumor volume was determined after combining multimodal CT images (contrast-enhanced scanning, axial slices of 0.6 mm) with preoperative MRI, PET. Spatial precise interstitial irradiation of the tumor volume was planned using special software. The duration of irradiation did not exceed 15 min. The light dose was from 150 to 200 J/cm^2. Transient clinical deterioration was recorded in about 2 patients (28.6%). These 2 patients had worsening neurological deficits in the early postoperative period (increase in hemiparesis from 4 points to 2 points in one patient and development of dysarthria and dysphasia in the second patient). The median overall survival from the first diagnosis of malignant glioma to death was 28.3 months. The median relapse-free survival was 13.1 months. MGMT status played a significant role in the outcome of patients treated with iPDT. Patients with a methylated MGMT promoter survived longer than patients with an unmethylated MGMT promoter by a median of 22.1 months, and they did not experience disease progression for an additional 9.3 months.

iPDT may be a promising treatment option in a population of patients at high risk of postoperative neurological deficit. It does not interfere with, but rather may complement, other treatment options for this disease, such as repeat radiation therapy and chemotherapy. iPDT remains a potential option for deep-seated gliomas in patients with high surgical risk and in case of tumor recurrence.

Key words: glioblastoma, interstitial photodynamic therapy, new technologies, results, glioma.

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ВОЗМОЖНОСТИ ИНТЕРСТИЦИАЛЬНОЙ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В ЛЕЧЕНИИ ГЛИОБЛАСТОМ ГОЛОВНОГО МОЗГА

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Резюме

Интерстициальная фотодинамическая терапия (иФДТ) — это минимально инвазивный метод лечения, основанный на взаимодействии света, фотосенсибилизатора (ФС) и кислорода. При глиомах головного мозга иФДТ включает стереотаксическое введение одного или нескольких световодов в целевую область для облучения опухолевых клеток и тканей, накопивших ФС, что вызывает в дальнейшем некроз и/или апоптоз опухолевых клеток, разрушение сосудистой сети опухоли и воспалительную реакцию, запускающую противоопухолевый иммунный ответ.

Целью исследования являлся анализ возможности применения иФДТ при лечении одноочаговых, небольших по размерам (до 3,5 см) глиобластом.
В исследование были включены 7 пациентов с одноочаговым вариантом глиобластомы с максимальным размером опухоли до 3,5 см и оценкой по шкале Карновского не менее 70 баллов. У 5 (71,4%) пациентов был рецидив глиобластомы, в 2 (28,6%) случаях опухоль была впервые диагностированной. В качестве ФС использовали фотодитазин, вводимый внутривенно капельно в дозе 1 мг/кг веса тела. Внутритканевое облучение выполняли с использованием лазера (Латус 2,5 (Аткус, Россия)) с длиной волны 662 нм и максимальной мощностью 2,5 Вт и цилиндрических рассеивающих волокон. Целевой объем опухоли определяли после объединения мультимодальных изображений КТ (сканирование с контрастным усилением, аксиальные срезы 0,6 мм) с предоперационной МРТ, ПЭТ. Пространственное точное внутритканевое облучение объема опухоли планировали с использованием специального программного обеспечения. Длительность облучения не превышала 15 мин. Световая доза составила от 150 до 200 Дж/см^2.
Транзиторное клиническое ухудшение было зафиксировано у 2 (28,6%) пациентов. У них наблюдали нарастание неврологического дефицита в раннем послеоперационном периоде (нарастание гемипареза с 4 баллов до 2 баллов у одного пациента и появление дизартрии и дисфазии у второго пациента). Медиана общей выживаемости от первого диагноза злокачественной глиомы до смерти составила 28,3 мес. Медиана безрецидивной выживаемости составила 13,1 мес. Статус MGMT сыграл значительную роль в результатах лечения пациентов с иФДТ. Пациенты с метилированным промотором MGMT жили дольше, чем пациенты с неметилированным промотором MGMT, в среднем на 22,1 мес, и у них не наблюдали прогрессирования заболевания в течение дополнительных 9,3 мес.
иФДТ может быть многообещающим вариантом лечения в популяции пациентов с высоким риском послеоперационного неврологического дефицита. Это не мешает, а скорее может дополнять другие варианты лечения данного заболевания, такие как повторная лучевая терапия и химиотерапия. иФДТ остается потенциальным вариантом при глубоко расположенных глиомах у пациентов с высоким хирургическим риском и при рецидиве опухоли.

Ключевые слова: глиобластома, интерстициальная фотодинамической терапии (иФДТ), новые технологии, результаты, глиома.

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Introduction

Glioblastoma (2021 WHO CNS, Grade IV) is the most common primary malignant tumor of the central nervous system [1-4]. Despite advances in oncology and the introduction of new methods and regimens for the treatment of malignant neoplasms of the central nervous system into clinical practice in recent decades, significant progress in achieving stable remission and increasing life expectancy in this category of patients has not been achieved [5-9]. A very low median overall survival of 12-16 months, persistent tumor resistance to drugs, and a high degree of diffuse, aggressive, and invasive tumor growth indicate that the treatment of glioblastomas remains a difficult task [10-17].

The current standard of treatment includes maximally safe tumor resection followed by adjuvant chemotherapy and radiotherapy [1, 2, 18-22]. Thus, even new advances in glioblastoma surgery (using fluorescence-guided surgery) have not fundamentally changed the prognosis of patients, and it still remains disappointing. In addition, patients with tumors localized in functionally significant or deep areas of the brain are often not prescribed surgical treatment using fluorescence navigation due to the high risk of aggravation or occurrence of neurological deficit in the postoperative period. To solve this problem and potentially prolong survival while maintaining adequate quality of life, several new approaches based on minimally invasive or non-invasive procedures such as brachytherapy, immunotherapy, radiosurgery, transcranial focused ultrasound or chemoradiation therapy have been investigated [4, 6, 9, 22-29].

Among these approaches, interstitial photodynamic therapy (iPDT) can be considered as a promising option based on the standard stereotactic procedure [30-33]. Patients receive PS orally or intravenously, which results in the appearance of the active substance in the intravascular space of the target tissue (tumor). Due to the dysfunction of the blood-brain barrier in the tumor area and impaired metabolism in tumor cells, PS selectively accumulates in malignant cells. Minimally traumatic access is performed from one trephination hole, no more than 1.5 cm in diameter. Then, along a pre-planned trajectory (stereotactic marking), the fibers of the optical diffuser are immersed in the target tumor tissue and the tumor is irradiated with a laser source. Excitation of PS by light causes the production of active oxygen species (in particular, singlet oxygen), which damage and ultimately destroy neoplastic cells. Compared to standard PDT, standard craniotomy is not required, and the tumor is accessed through a trephination hole. Thus, dead tumor tissue remains inactivated *in situ* [34-41]. Another advantage of the method is that normal brain tissue is preserved due to the selective accumulation of PS in the tumor (Fig. 1).

The effects of iPDT on tumor tissue and its environment are still being studied due to the abundance of processes involved. In particular, the activation of the immune response to the use of PDT plays a significant role. At

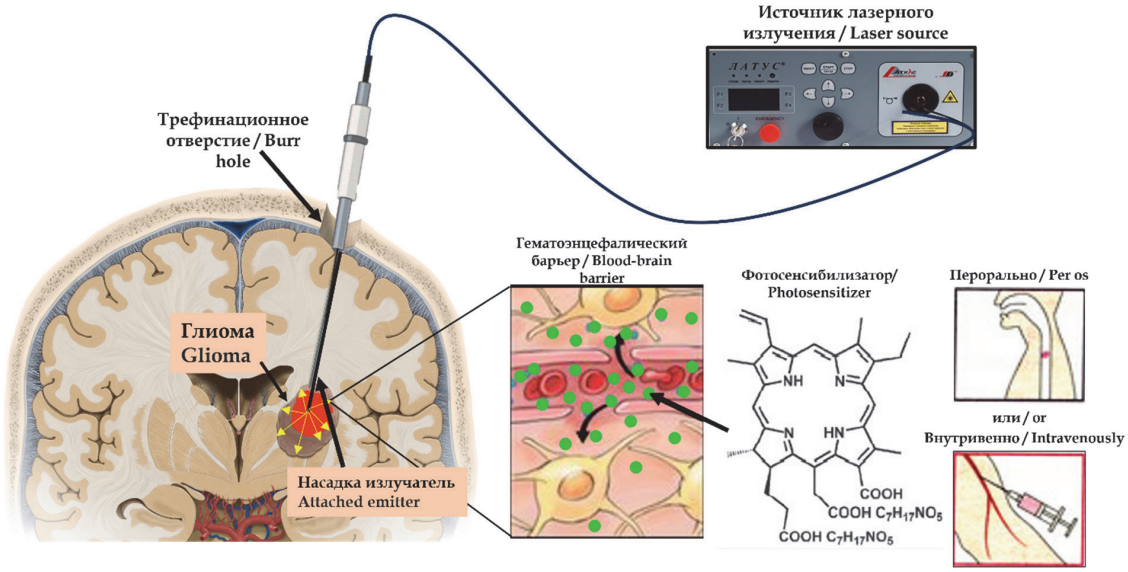

Рис. 1. Блок схема метода интерстициальной фотодинамической терапии.
Fig. 1. Block diagram of the interstitial photodynamic therapy method.

present, there is a relatively small number of clinical studies describing the use of this technique in patients with glioblastoma and presenting long-term results of the study after its use [3, 8, 11, 25, 42-46].

To determine the capabilities of this technique, we studied the intraoperative iPDT and the long-term results of its use in a cohort of patients with glioblastoma.

Materials and Methods

A single-center, cohort prospective study with elements of retrospective analysis was conducted at the Department of Neurooncology of the Russian Research Institute of Neurosurgery named after prof. A.L. Polenov. The study included 7 patients of different genders and ages.

All patients signed voluntary informed consent to participate in the study in accordance with Good Clinical Practice (GCP) (Clinical Trials Directive 2001/20/EC; GCP Directive 2005/28/EC; Clinical Trials Regulation 536/2014; Executive Commission (Regulation 2017/556)), Good Manufacturing Practice (GMP) standards and the principles of the Helsinki Declaration, 7th revision of 2013. The study was approved by the local ethics committee at the Russian Research Institute of Neurosurgery named after prof. A.L. Polenova No. 4 from 12/17/2013.

The inclusion criteria for the study were:

- written informed consent;
- age 18–75 years;
- Karnofsky performance status (KPS) ≥70 points;
- radiologically suspected diagnosis (according to RANO criteria [47]) of the first recurrence of glioblastoma located in the cerebral hemisphere, including the insular and intermediate lobes of the brain; tumors in the brainstem were excluded; the first MRI (magnetic resonance imaging) with signs of first recurrence (radiological RANO criteria for disease progression [47]) within 8 weeks before informed consent, not necessarily identical to the primary tumor location, or primary glioblastoma with deep localization without the possibility of complete tumor removal due to the high risk of postoperative neurological deficit;
- single or single progressive presence of contrast enhancement according to MRI, the largest tumor diameter no more than 3.5 cm.

Exclusion criteria:

- multifocal disease (more than 2 sites);
- patients with significant non-contrasting areas of tumor;
- previous treatment for relapse;
- presence of another malignancy;
- hypersensitivity to porphyrins;
- porphyria;
- HIV infection, active hepatitis B or C infection;
- patients with poor prognosis, such as severe ischemic heart disease, heart failure (NYHA III/IV), severe poorly controlled diabetes, immunodeficiency, residual neurological deficit after stroke, severe mental retardation or other serious concomitant systemic disorders incompatible with the study;
- any active infection;
- any psychological, cognitive, family, social condition that, in the opinion of the researcher, compromises the patient's ability to understand health information and the procedure, to give informed consent or to comply with the study protocol;
- previous antiangiogenic therapy;
- participation in another interventional clinical trial

during this study or within 4 weeks before the start of this study;
- pregnancy or breastfeeding.

The tumor size did not exceed the maximal extension of 3.5 cm, determined by gadolinium enhancement of the tumor on T1-weighted MRI. Viability of the tumor tissue was previously confirmed by a minimally invasive stereotactic biopsy procedure with subsequent morphological examination to exclude treatment-related effects or pseudoprogression of the tumor. The size limitation was based on the maximum number of light fibers per laser, since the optimal distance between

Таблица 1
Клиническая характеристика пациентов
Table 1
Clinical characteristics of patientsy

Характеристики пациентов с иФДТ Characteristics of patients with iPDT	Пациент Patient						
	1	2	3	4	5	6	7
Возраст (лет) **Age (years)**	45	61	47	58	53	60	49
Пол **Gender**	м m	м m	ж f	м m	ж f	м m	ж f
Индекс Карновского **Karnofsky index**	80	80	90	80	80	80	90
Симптомы заболевания **Symptoms of the disease**							
общемозговая симптоматика general cerebral symptoms	+	+	+	+	+		+
судорожный синдром convulsive syndrome	+						
афазия без парезов aphasia without paresis	+				+		
парез без афазии paresis without aphasia		+				+	
афазия и парез aphasia and paresis							
Сторона полушария **Side of the hemisphere**	правая right	левая left	правая right	правая right	левая left	левая left	правая right
Локализация, доля мозга **Localization, brain lobe**							
лобная frontal			+				
височная temporal	+				+		
теменная parietal		+					+
затылочная occipital						+	
таламическая область thalamic region				+			
Клиническая характеристика опухоли **Clinical characteristics of the tumor**							
Максимальный размер опухоли, мм **Maximum tumor size, mm**	29	25	20	23	19	22	27
первичная опухоль primary tumor		+			+		
первый рецидив опухоли first tumor recurrence	+		+	+		+	+

Степень злокачественности опухоли по ВОЗ **Grade,WHO**	IV	IV	IV	IV	IV	IV	IV
Степень ВОЗ при первоначальном диагнозе **WHO grade at primary diagnosis**	IV		IV	IV		IV	IV
Статус метилирования промотора MGMT **MGMT promoter methylation status**							
метилированный methylated	+				+	+	
неметилированный unmethylated		+	+	+			+
Мутация IDH **IDH mutation**							
дикий тип wild type	+		+	+	+	+	+
мутировал mutated		+					
Время пребывания в стационаре, дни **Duration of hospital stay, days**	6	5	7	5	4	5	6
Количество операций **Number of operations**	3	2	2	3	2	2	3
Лучевая терапия, СОД Гр **Radiation therapy, STD Gr**	60	120	180	120	60	90	120
Гамма нож, Кибер нож **Gamma knife, Cyber knife**		да / yes		да / yes			
Химиотерапия **Chemotherapy**							
первая линия, количество курсов first line, number of courses	7 тмз 7 tmz	5 тмз 5 tmz	10 тмз 10 tmz	8 тмз 8 tmz	7 тмз 7 tmz	11 тмз 11 tmz	9 тмз 9 tmz
вторая линия, количество курсов second line, number of courses	2 тмз + авастин 2 tmz + avastin	PCV	ломустин + винкристин lomustine + vincristine	3 тмз + авастин 3 tmz + avastin	PCV	авастин + иринотекан avastin + irinotecan	4 тмз 4 tmz
третья линия, количество курсов third line, number of courses	3 тмз 3 tmz		авастин + иринотекан avastin + irinotecan	PCV			PCV
Безрецидивная выживаемость, мес **Progressive-free survival (PFS), months**	15	10	9	6	12	29	11
Общая выживаемость, мес **Overall survival (OS), months**	36	19	21	17	28	61	22

light diffusers is about 7–9 mm, which is necessary for precise tissue irradiation without causing critical thermal effects. Detailed clinical characteristics of the patients are presented in Table 1.

Technique of the conducted interstitial photodynamic therapy

Photoditazine (OOO Veta-Grand, Russia) (Fig. 2A) with the active substance chlorin e6, diluted in 200 ml of physiological solution at the rate of 1 mg of the drug per 1 kg of the patient's body weight, administered to the patient intravenously 2 hours before the expected placement of the trephination hole for PDT, was used as the PS.

Preoperative planning was performed using software for spatially precise intra-tissue irradiation of the tumor volume. The target tumor tissue volume to be irradiated was determined after combining multimodal CT (computed tomography) images (contrast-enhanced

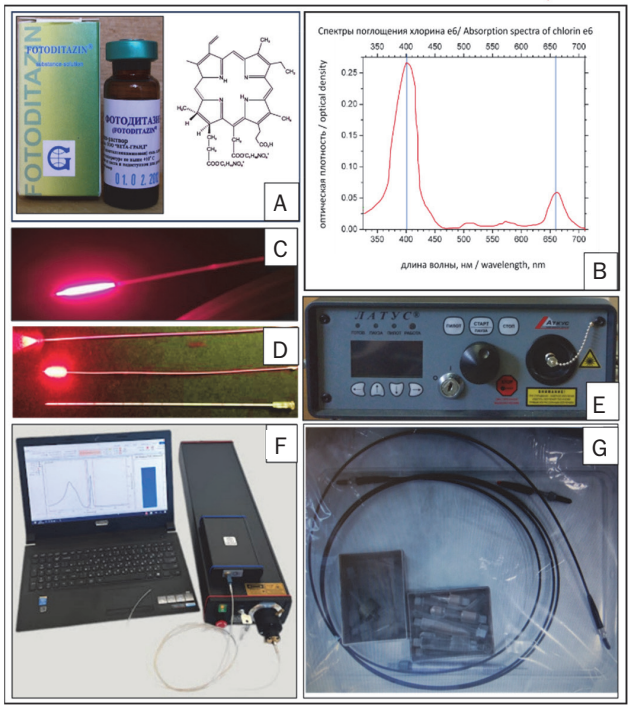

Рис. 2. Оснащение для иФДТ: А – фотодитазин; В – спектр поглощения хлорина е6; С – цилиндрический диффузор лазерного излучения в рабочем состоянии; D – формы диффузоров; Е – источник излучения полупроводниковый лазер «Латус 2,5»; F – спектроанализатор ЛЭСА-01-БИОСПЕК; G – световод.
Fig. 2. Equipment for iPDT: A – photoditazine; B – absorption spectrum of chlorin e6; C – cylindrical diffuser of laser radiation in working condition; D – shapes of diffusers; E – radiation source semiconductor laser "Latus 2.5"; F – spectrum analyzer LESA-01-BIOSPEC; G – light guide.

scanning, 0.6 mm axial slices) with preoperative gadolinium-enhanced MRI and PET-CT (positron emission tomography) (Fig. 3). The images were loaded into a computer and processed using the Gamma Multivox 2D/3D automated workplace software (AWP) for image summation and construction of a 3D tumor model.

At the next stage, simulations were performed for the iPDT parameters taking into account the obtained tumor volume and its spatial location according to the 3D simulation at the previous stage. Thus, for iPDT simulation, the software of the integrated Monte Carlo simulation platform was used for light delivery from the laser source and control of the thermal effect from laser radiation exposure. Figure 4A shows an overview of the integrated Monte Carlo simulation platform. The simulation platform processes the parameters from the user and performs an analysis of heat dissipation, light propagation and energy absorption. It is possible to determine the best PDT mode, which will be most effective for activating the photosensitizer. The software of the integrated Monte Carlo simulator made it possible to carry out iPDT taking into account five important criteria, including: the degree of light penetration; the rate of energy absorption; the level of uniform energy absorption in the tumor tissue; the time required to deliver the target volume of light energy; the range of temperature change.

Thus, using the software interface based on the integrated Monte Carlo modeling platform, a numerical analysis of the propagation and absorption of light (photon) and heat dissipation in the brain tissue and tumor (Fig. 4A, B) was performed. The platform allowed to select the number of laser radiation sources, the light spectrum (wavelength of the radiation spectrum), and the formation of an integrated analysis of the obtained data, taking into account the photosensitizer. Using the program, results for assessing heat dissipation, light absorption, and delivery of light energy to the target tissue were obtained, which made it possible to select the most effective iPDT mode. Figures 4B–F show the results for the photosensitizer chlorin e6 (photoditazine), which has an absorption peak at 400 and 662 nm, respectively. For the calculations, we used a three-dimensional spherical tumor model obtained from the preoperative

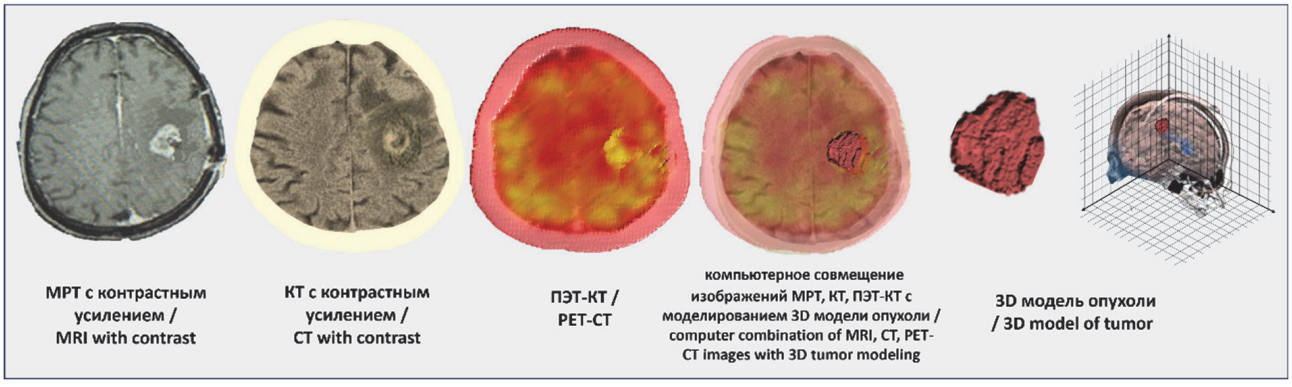

Рис. 3. Планирование предполагаемого объема облучения по данным нейровизуализационных методик с последующей суммацией изображений и построения 3D модели, загрузкой последней в программное приложение для расчета параметров иФДТ и интраоперационного планирования доступа к опухоли.
Fig. 3. Planning the expected volume of irradiation based on neuroimaging data, followed by image summation and construction of a 3D model, loading the latter into a software application for calculating iPDT parameters and intraoperative planning of access to the tumor.

3D modeling data. Figure 4C shows heat maps and heat dissipation graphs depending on the wavelength under constant (upper figure) and cyclic illumination (lower figure). The results showed that there was no detectable temperature change at any given setting, limiting damage to surrounding normal brain tissue due to thermal scattering from the laser sources during device operation in the cycling setting. Figures 4E,F summarize the performance comparisons across five criteria (degree of light penetration into target tumor tissue; energy absorption rate; level of energy absorption uniformity across the tumor volume; time required to deliver the target light energy; and range of temperature change) and show the light absorption distribution across the tumor volume for chlorin e6 (Figure 4E). We specified and calculated these variables in the simulations to provide detailed information on the critical variables in obtaining the results. Specifically, we assessed the ability of light to penetrate different types of media, such as gray and white matter, perifocal brain edema, and tumors (including cystic and solid components), for each light source. The energy absorption coefficient in the tumor was calculated in accordance with the light spectra, as well as the time to reach the threshold energy significant for tumor growth suppression. The results obtained under different conditions (wavelength) showed that the optimal condition for chlorin e6 is achieved with a combination of wavelengths of 400 and 662 nm and 25% of the irradiation working cycle.

The actual iPDT technique was as follows. After accessing the tumor along a special, pre-set trajectory of preoperative marking, an intraoperative analysis was performed for the presence of photosensitizer accumulation in the tumor tissue and the intensity of its luminescence. After receiving a positive result (maximum light emission by chlorin e6), a biopsy of the tumor was taken and sent to the histological express laboratory at the research laboratory of pathomorphology of the nervous system of the Russian Scientific Research Institute named after prof. A.L. Polenov located in the same building. Within 15-20 minutes, the morphological result of the biopsy was obtained. After confirmation that

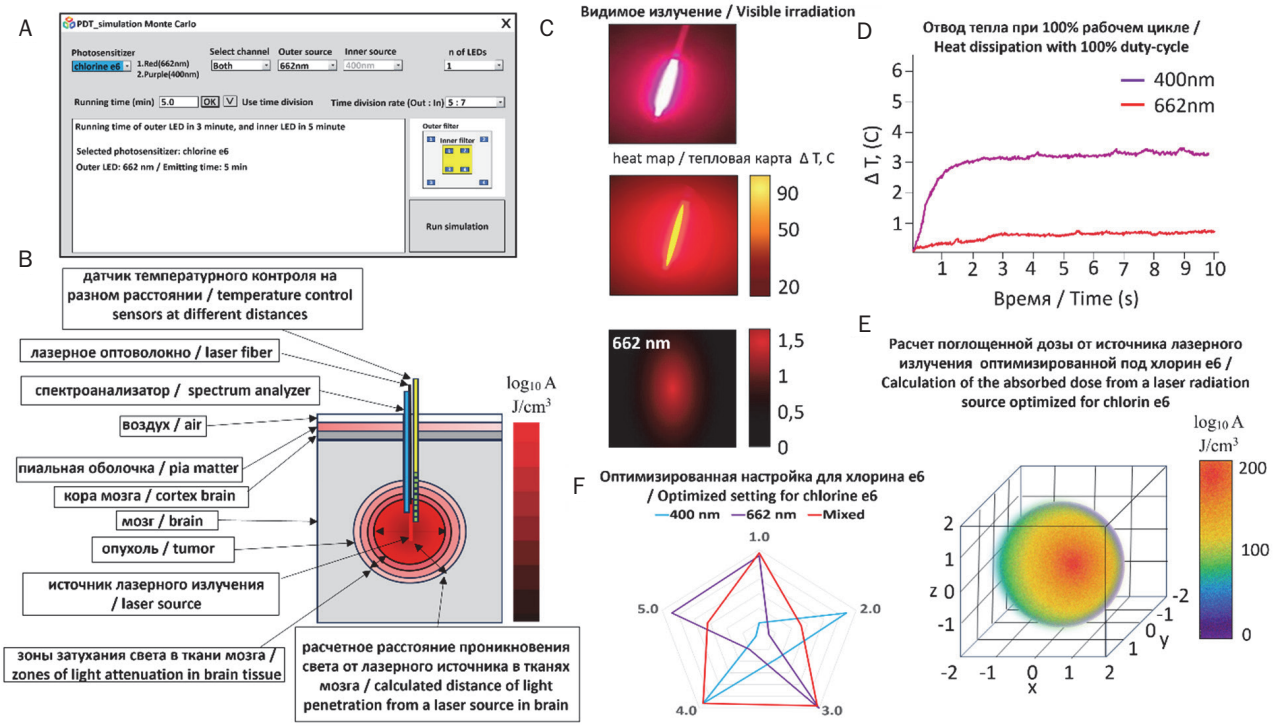

Рис. 4. Схема моделирования параметров для проведения сеансов иФДТ: A – обзор интегрированного симулятора программного обеспечения для проведения иФДТ – PDT simulation Monte Carlo; B – поперечное сечение модели опухолевой ткани для расчета проведения сеанса иФДТ и контроля параметров; C – рассеивание света и тепловая карта на длине волны 662 нм для активации хлорина е6; D – график температуры отведения тепла в режиме полноценного рабочего цикла; E – расчет поглощенной дозы от источника лазерного излучения в зависимости от расстояния от источника излучения, и учета эффекта затухания света в мозговой ткани; F – лучший режим иФДТ для активации хлорина е6 с учетом оптимизации.

Fig. 4. Schematic diagram of the simulation of parameters for conducting iPDT sessions. A – overview of the integrated software simulator for conducting iPDT – PDTsimulation Monte Carlo; B – cross-section of the tumor tissue model for calculating the iPDT session and parameter control; C – light scattering and heat map at a wavelength of 662 nm for the activation of chlorin e6; D – graph of the heat removal temperature in the full-duty cycle mode; E – calculation of the absorbed dose from the laser source depending on the distance from the radiation source, and taking into account the effect of light attenuation in the brain tissue; F – the best iPDT mode for chlorin e6 activation taking into account the optimization.

the biopsy material contained a tumor (glioblastoma), the next stage of iPDT was performed. Thus, the viability of tumor tissue was confirmed before iPDT using a minimally invasive stereotactic biopsy procedure with subsequent morphological examination to exclude treatment-related effects or tumor pseudoprogression.

When planning the procedure for introducing the laser radiation source with subsequent tumor irradiation, special equipment was used. Technically, the procedure was feasible in all expected cases. Intratissue irradiation was performed (from the target point with maximum luminescence emission according to spectroscopy data) using a laser (Latus 2.5 (Atkus, Russia)) (Fig. 2E) with a wavelength of 662 nm and a maximum power of 2.5 W, an optical fiber cable (Fig. 2D) and using cylindrical scattering fibers (Fig. 2C). The fibers for delivering light from the laser radiation source consisted of 4-6 cylindrical diffusers with a diameter of 600 μm and a length of 20 or 30 mm. The length of the diffuser was at least equal to the extent of the tumor along the trajectory of introduction. These fibers were introduced into the tumor tissue using a stereotaxic approach. The energy illumination was assessed using the "Optical power meter QB230" (ADVANTEST Corp., Japan).

Using the intraoperative spectral online monitoring technique (LESA-01-BIOSPEC laser electron-spectral system (Russia) (Fig. 2F)), it was possible to monitor the transmission of emitted light between the fibers and the fluorescent light of chlorin e6. The system consists of a laser source for excitation of the photosensitizer and a miniature universal spectrometer for recording and analyzing the fluorescent signal. During most irradiation sessions, chlorin e6 fluorescence before illumination was characterized as "good" and then decayed during irradiation. This fact, at least in cases with good postoperative gradation of light transmission, indicated a significant consumption of chlorin e6, as expected, due to photobleaching of this photosensitizer. The technique of spectral online monitoring allowed local determination of the degree of accumulation of the photosensitizer in the tumor tissue and normal brain tissue accessible to the fiber-optic probe. For the assessment, special software running in the Windows operating system was used, which made it possible to compare the degree of accumulation of the photosensitizer in the tumor tissue with the standard or with normal brain tissue. The procedure for collecting tissue samples was carried out under the guidance of intraoperative smear preparations, which usually guaranteed the selection of both solid and necrotic areas of the tumor. For histopathological examination, tissue probes were used and the density of tumor cells, the presence of necrosis, vascular proliferation, tissue proliferation of the tumor (Ki-67 index, P53), and molecular genetic analyses, such as determining the methylation status of the MGMT promoter, and IDH status were analyzed.

At each target point (according to both preoperative planning and intraoperative spectroscopy data) along

Таблица 2
Индивидуальные параметры лазерного излучения
Table 2
Individual parameters of laser radiation

Пациент Patient	Вариант глиобластомы Variant of glioblastoma	Доза ФС мг/кг Dose of PS mg/kg	Длина волны излучения, нм Radiation wavelength, nm	Диаметр оптического волокна, мкм Optical fiber diameter, microns	Выходная оптическая мощность, Вт Output optical power, W	Экспозиционная доза света в Дж/см^2 / Exposure dose of light in J/cm^2	Плотность мощности излучения в мВт/см^2 Radiant power density in mW/cm^2	Время облучения, мин. Irradiation time, min.	Число использованных световодов Number of used light diffusers
1	рецидив recurrence	1	665	600	2	200	200	15	6
2	первичная primary	1	665	600	3	150	200	9	4
3	рецидив recurrence	1	665	600	2	200	200	15	6
4	рецидив recurrence	1	665	600	2	180	200	11	5
5	первичная primary	1	665	600	3	150	200	9	4
6	рецидив recurrence	1	665	600	3	180	200	11	5
7	рецидив recurrence	1	665	600	3	200	200	15	6

the route of the light emitter, at least one irradiation session was performed. In case there was a residual level of photosensitizer accumulation after irradiation, according to spectroscopy data, a repeat irradiation session was performed in this area. The total irradiation duration did not exceed 15 min (Fig. 2G). The exposure dose of light was calculated based on the geometry and size of the tumor using the integrated Monte Carlo modeling platform. The light dose averaged 180 J/cm^2 (Table 2).

After the session, to avoid light damage to the retina due to the presence of traces of chlorin e6, the patient was in opaque glasses and a dimly lit room for the next 24 hours.

Assessment of the safety and tolerability of the treatment method

Complications that developed during iPDT treatment were considered any postoperative complications that developed within 2 months after surgery. The severity of the reaction and frequency were assessed in accordance with the unified terminology criteria for assessing the severity of adverse events (CTCAE) (version 5) dated 11/27/2017 [48]. In the postoperative period, the patient's complaints were assessed (daily, until discharge), somatic (including dermatological manifestations) and neurological status (daily, until discharge), ophthalmologist examination (at least 2 times before discharge, 1 and 2 months after surgery), electroencephalogram and electrocardiogram (at least 1 time before discharge) were assessed. Laboratory tests (clinical blood test, clinical urine test, biochemical blood test, coagulogram) were also performed on the 1st, 3rd and 7th day after surgery, before discharge from the hospital, 1 month and 2 months after surgery.

Statistical analysis

All analyses were performed using SPSS (version 20, IBM Corp.). Descriptive survival was analyzed using the Kaplan-Meier method, p-values <0.05 were considered significant.

Results

Before iPDT fiber placement, 7–13 tissue samples were collected along one of the planned treatment trajectories. 3–7 samples were used for histopathological evaluation and molecular genetic analysis, and 4–9 samples were collected for chlorin e6 concentration studies. The diagnosis of glioblastoma was morphologically verified in all patients.

Fluorescence intensity was analyzed in all patients. Almost all patients had high chlorin e6 fluorescence before irradiation, which also showed high chlorin e6 concentration in the extracted tissue, in parts of the tumor. The mean chlorin e6 concentrations measured along the biopsy trajectories ranged from 1.5 to 3.1 μM. The strongest chlorin e6 fluorescence intensity was found in patient 1, which was consistent with the chlorin e6 extraction values in the biopsy tissue, which were also among the highest among all patients. Slight chlorin e6 fluorescence was found in one patient, although one tissue sample showed a high chlorin e6 concentration. This tumor was characterized by an extensive area of necrosis.

Spectral measurements performed before and after iPDT showed high chlorin e6 fluorescence before irradiation and very low chlorin e6 fluorescence after irradiation, indicating significant photobleaching.

Postoperative MRI image analysis

Postoperative MRI performed within 24 h after iPDT showed minimal (3 patients (42.9%)) or no (4 patients (57.1%)) contrast enhancement in the iPDT treated area, at a distance of about 15 mm from the irradiation center.

Various pre-processing techniques were applied before image analysis. First, MRI data recorded at different time points were positionally aligned with each other. This was done automatically using the Gamma Multivox 2D/3D AWP software package, followed by manual checks and adjustments. All images, settings and segmentations were reviewed by experienced neuroradiologists. Figure 5 shows as an example the regions of interest in one patient, such as the tumor volume (consisting of the contrast enhancement area in T1 mode and the necrosis area), the perifocal edema area, the expected iPDT effect area and the area of changes after iPDT. The PDT effect area appeared after the PDT session.

Segmented volumes were rounded to the nearest 3 mm, since higher accuracy was not meaningful based on the physical resolution of the image. The necrosis-to-tumor ratio (NTR) was calculated for each case before treatment by dividing the necrosis volume by the tumor volume, according to Henker C. et al. [19].

Thus, the volume of tissue exposed to phototoxic effects from laser radiation was determined based on postoperative MRI data. The average calculated size of the phototoxic effect from one diffuser fiber was 3.1 × 2.7 × 2.8 cm. The average total target volume of involved tumor tissue from one diffuser was 3.57 ± 0.32 cm^3.

Immediate results

Transient clinical deterioration was recorded in 2 patients (28.6%), which was mainly due to increased perifocal edema and/or some hemorrhagic imbibition in the irradiation zone in the early postoperative period. However, these changes were not associated with direct traumatic effects due to the individual trajectory of the laser tip and tumor vessels. These patients showed an increase in neurological deficit in the early postoperative period (an increase in hemiparesis from 4 points to 2

points in one patient and the appearance of dysarthria and dysphasia in the second patient). Only one patient with hemiparesis showed an increase in neurological deficit after surgery, which persisted for more than 5 weeks. However, the symptoms significantly regressed within 5 weeks after iPDT even without hormonal therapy, which was avoided in order not to interfere with the possible immunological effects of PDT. Moreover, the development of postoperative complications did not depend on the volume of the tumor.

Adverse reactions associated with the use of photoditazine according to the CTCAE criteria were not detected in patients, which can be explained by the small group of patients.

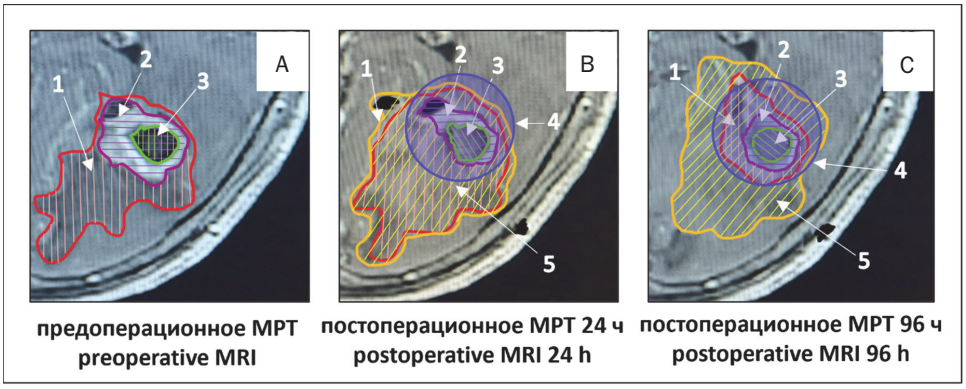

Рис. 5. Оценка МРТ до и после иФДТ, показанная в качестве примера у одного пациента. Сегментированные объемы, обозначенные цветовыми наложениями на изображениях МРТ (Т1-режим) (1 – зона перифокального отека (красная), 2+3 – объем опухоли с усилением контраста в Т1-режиме (2 – солидный компонент (фиолетовый), 3 – зона некроза (зеленый)), 4 – предполагаемая зона воздействия от иФДТ (синий), 5 – зона изменений по данным МРТ после иФДТ (желтый)).
Fig. 5. MRI evaluation before and after iPDT, shown as an example in one patient. Segmented volumes indicated by color overlays on MRI images (T1-weighted) (1 – area of perifocal edema (red), 2+3 – tumor volume with contrast enhancement in T1-weighted (2 – solid volume (purple), 3 – necrosis volume (green)), 4 – estimated area of iPDT effect (blue), 5 – area of changes according to MRI data after iPDT (yellow)).

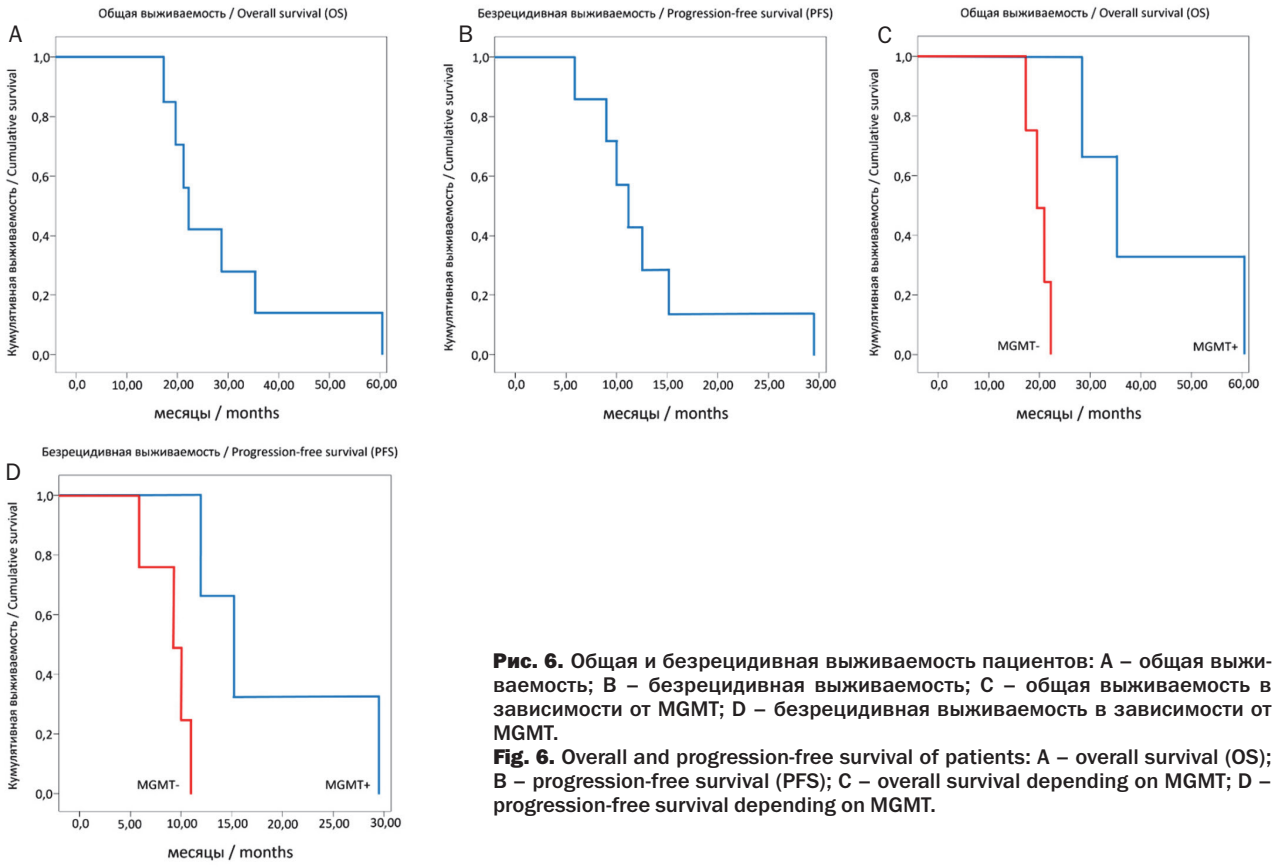

Рис. 6. Общая и безрецидивная выживаемость пациентов: A – общая выживаемость; B – безрецидивная выживаемость; C – общая выживаемость в зависимости от MGMT; D – безрецидивная выживаемость в зависимости от MGMT.
Fig. 6. Overall and progression-free survival of patients: A – overall survival (OS); B – progression-free survival (PFS); C – overall survival depending on MGMT; D – progression-free survival depending on MGMT.

Remote results

Catamnesis was monitored in all patients. The duration of observation after iPDT was up to 61 months. The cause of death was tumor progression. The median overall survival from the first diagnosis of malignant glioma to death was 28.3 months. The median relapse-free survival was 13.1 months. The median time between the first diagnosis and the course of iPDT was 10.8 months.

MGMT status played a significant role in the outcome of patients with iPDT. Patients with MGMT promoter methylation survived longer than those with unmethylated MGMT by a median of 22.1 months (based on median overall survival) and remained progression-free for an additional 9.3 months (based on median relapse-free survival) (Fig. 6C,D). The median overall survival for patients with MGMT promoter methylation was 41.3 months, while for patients with unmethylated MGMT it was 18.6 months ($p<0.005$). The median relapse-free survival was 18.6 months for patients with MGMT promoter methylation and 9.3 months for patients with unmethylated MGMT ($p<0.005$). This is usually explained by a higher sensitivity of tumor cells to adjuvant chemotherapy with temozolomide. In cases of relapsed glioblastoma treated with iPDT, no survival advantage was found for the methylated MGMT promoter compared to the unmethylated MGMT promoter. This may be due to higher resistance of the tumors of these patients to chemotherapy due to inhibition of apoptosis or upregulation of genes causing multidrug resistance.

Clinical example

Patient K., 45 years old, first relapse of glioblastoma after surgical treatment, 60 Gy RT course, temozolomide chemotherapy. iPDT with chlorin e6 was performed with assessment of photosensitizer accumulation in tumor tissue during surgery and assessment of fluorescence intensity according to spectroscopy data. MRI images with gadolinium contrast enhancement in T1 mode before and 24 hours after surgery and 3 months after surgery are presented below (Fig. 7).

Discussion

Glioblastoma is the most difficult to treat of all primary brain tumors. Factors determining the prognosis of this disease include such factors as age and working capacity status before treatment, the volume of tumor resection during surgery, the volume of postoperative radiation therapy and chemotherapy, and molecular genetic factors of the tumor [1, 2, 7, 9, 14, 29, 41]. The extremely low median survival time in patients with glioblastoma indicates that there is currently no effective treatment for this category of patients. To improve the

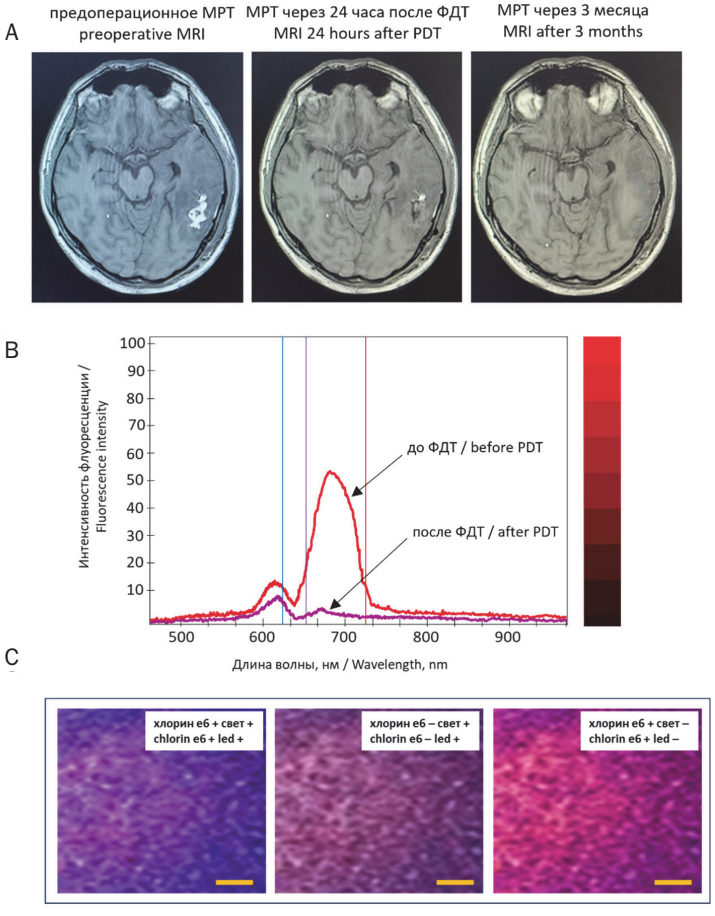

Рис. 7. Клинический пример пациент: А – МРТ головного мозга 1,5 Тесла с контрастным усилением гадолинием (перед операцией, через 24 ч после операции и через 3 мес после операции) аксиальные срезы; В – спектральный анализ флуоресценции в области целевой опухолевой ткани (до ФДТ, и после ФДТ в дозе 180 Дж/см^3); С – биопсийный материл опухоли полученный *in vivo* до иФДТ был быстро обработан, зафиксирован в 4% параформальдегиде, залит в парафин, нарезан на микротоме и подвергнут окрашиванию гематоксилином-эозином (H&E); масштабная линейка 50 мкм. Представленные изображения выполнены в 3 режимах: в режиме обычного света и под источником синего цвета (позволяющего видеть флуоресценцию хлорина е6 в ткани опухоли); в режиме только обычного света, без источника синего света; в режиме отсутствия обычного освещения, но в режиме синего цвета позволяющего видеть флуоресценцию хлорина е6.

Fig. 7. Clinical example of a patient: A – MRI of the brain 1.5 Tesla with contrast enhancement with gadolinium (before surgery, 24 hours after surgery, and 3 months after surgery) axial sections; B – spectral analysis of fluorescence in the area of the target tumor tissue (before PDT, and after PDT at a dose of 180 J/cm^3); C – tumor biopsy material obtained *in vivo* before iPDT was rapidly processed, fixed in 4% paraformaldehyde, embedded in paraffin, cut on a microtome and stained with hematoxylin and eosin (H&E); scale bar 50 μm. The presented images were obtained in 3 modes: in normal light mode and under a blue light source (allowing to see chlorin e6 fluorescence in the tumor tissue); in normal light only mode, without a blue light source; in the absence of normal lighting, but in the blue light mode allowing one to see the fluorescence of chlorin e6.

prospects for patients with glioblastoma, it is necessary to provide a larger range of treatment methods against this malignant tumor in the future [2, 9, 11, 18].

According to the literature, 90–95% of all glioblastomas recur within 2 cm of the primary tumor margin. The remaining 5–10% of recurrences beyond this 2-cm margin can be called distant recurrences. The high rate of local recurrences may be due to insufficient local eradication of tumor cells. One explanation may be that the tumor margins visible on conventional MRI do not include tumor cells disseminated into the surrounding tissues of the perifocal zone [5, 9, 19, 28, 33, 38].

At the present time, the first step of treatment is to perform the safest possible resection in order to remove as much of the tumor as possible and to avoid the development of neurological deficit. PDT is one of the methods studied in recent decades, which allows increasing the radicality of the surgical intervention, with a minimal risk of complications, and has recently been increasingly used in neurosurgical practice. The effect of PDT is based on the destruction of tumor cells through a complex mechanism of direct cellular damage caused by singlet oxygen generated by the excitation of the photosensitizer accumulated inside the tumor cells, as well as indirect effects such as damage to the intima in microvessels inside the tumor, embolic mechanisms caused by blood stagnation due to spasm of arterioles, and inflammatory reactions of immune cells [6, 8, 9, 11, 17, 25].

The current issues related to iPDT that remain at the present time are: selection of a light diffuser with suitable geometry for the application of optimal photostimulation of tumor tissue; determination of the optimal number of diffusers for introduction into the tumor in order to maximize the therapeutic effect while minimizing the harm associated with the introduction of the diffuser through normal brain tissue; the correct choice of tumors of suitable size, anatomical location and geometry for greater safety and effectiveness of iPDT [12, 14, 19, 27, 29, 35, 38].

Another problem with iPDT is the uniform delivery of photostimulation to achieve adequate energy flux to the maximum tumor volume without causing thermal damage to normal brain tissue. Model experiments studying light delivery have determined the optimal geometry of light guides for iPDT. Cylindrical light diffusers have a larger emitting surface area with a lower energy flux velocity at the tissue/light emitter interface than flat split fibers [27]. Thus, light delivery through a cylindrical diffuser improves photon distribution with reduced sensitivity to local tissue absorption variability, thereby distributing the radiation over a larger tissue volume than flat split fibers. However, the light flux falls faster from a flat fiber, which is useful when treating a tumor in close proximity to functionally significant areas of the brain. Thus, the light diffuser geometry as well as the total number of diffusers required to safely treat the tumor are factors that should be considered preoperatively to achieve optimal iPDT [33, 38, 42].

The dose of light delivered during iPDT is another important factor in this technique. The applied dosimetric model should take into account the type of photosensitizer. At the same time, to achieve the maximum therapeutic effect of iPDT, it is necessary to calculate the flow rate to achieve maximum photobleaching of the photosensitizer in the tissue (more than ≥95%). Thus, in the case of iPDT with 5-aminolevulinic acid (5-ALA), modeling shows that maximum photobleaching is achieved at a distance of about 4 mm from the surface of the light diffuser emitting a power of 200 mW/cm^2 for 1 h. Based on the expected volume of tissue affected by photoirradiation, the optimal interfiber distance of photodiffusers in iPDT should be about 10 mm, and the maximum photostimulation power should not exceed 200 mW/cm^2, since the threshold value at which the risk of tissue temperature increasing above 48°C (the threshold at which thermal side effects become a factor) increases significantly [4, 30].

Software for optimizing iPDT delivery has been developed over several decades [16]. One of the approaches uses co-registration of contrast-enhanced magnetic resonance imaging and positron emission tomography with stereotactic computed tomography images to provide virtual trajectory planning and positioning of light scatterers within the tumor [30]. The goal is to virtually plan the implantation of the optimal number of light scatterers to ablate the tumor without damaging adjacent vasculature or traversing functionally important brain areas.

In this study, we explored the potential of iPDT as part of a combination treatment for glioblastoma to motivate scientists and clinicians to further study this promising therapeutic option. iPDT is applied by stereotactically inserting a fiber optic cable into the tumor and delivering a photoemitter (laser light source) to the tumor tissue after pre-injection of a photosensitizer into the patient. The use of iPDT is similar to laser interstitial thermal therapy (LITT) for the treatment of glioblastoma, as both are minimally invasive stereotactic methods, but iPDT has the additional advantage of selectively targeting tumor cells [6, 8, 9, 11, 17, 28, 37, 39].

Analyzing the data of the research results, as well as data from available literary sources reporting on the use of iPDT as one of the methods in the treatment of glioblastoma, it is quite difficult to conduct a direct meaningful comparison of them, due to the pronounced heterogeneity of the treatment groups in different studies. The results of using the iPDT technique in patients with malignant gliomas depending on the year of work, the type of photosensitizer and the PDT parameters of some studies are presented in Table 3.

In our cohort of patients treated with iPDT, 5 of 7 patients had distant recurrence (outside the site of iPDT).

Таблица 3
Результаты использования и ФДТ у пациентов со злокачественными глиомами у разных авторов

Table 3
Results of the use of iPDT in patients with malignant gliomas by different authors

Авто Author	Год Year	Количество пациентов Number of patients	Гистология Histology	Фотосенсибилизатор Photosensitizer (PS)	Способ введения ФС Method of administration of PS	Время от введения ФС до операции Time from PS administration to surgery	Доза ФС, мг/кг Dose of PS, mg/kg	Длина волны, нм Wavelength, nm	Доза облучения, Дж/см^3 Radiation dose, J/cm^3	Медиана общей выживаемости, мес Median overall survival (OS), months	Медиана выживаемости без прогрессирования, мес Median progression-free survival (PFS), months
Muller P.J. [35]	1990	40	22 ГБМ 18 АА 22 GBM 18 AA	Гематопорфирин Hematoporphyrin	внутривенно intravenously	18 – 24	2 – 5	630	8 – 175	8,5 (6,5 – 17,1)	нет данных n/a
Powers S.K. [45]	1991	6	1 ГБМ 1 ГС 4 АА 1 GBM 1 GS 4 AA	Гематопорфирин Hematoporphyrin	внутривенно intravenously	24	2	630	400	0,5 – 11	нет данных n/a
Origata-mo T.S. [37]	1993	15	8 ГБМ 6 АА 1 ОА 8 GBM 6 AA 1 OA	Гематопорфирин Hematoporphyrin	внутривенно intravenously	48 – 72	2	630	50	8 – 16	нет данных n/a
Kostron H. [46]	1996	50	ГБМ GBM	Гематопорфирин Hematoporphyrin	внутривенно intravenously	24 – 72	2,5	630	15 – 260	10 ГР 19 ГП 10 GR 19 GP	13
Muller P.J. [9]	1996	20	11 ГБМ 9 АА 11 GBM 9 AA	Гематопорфирин Hematoporphyrin	внутривенно intravenously	12 – 36	2	630	15 – 110	9,2 ГБМ 12 АА 9,2 GBM 12 AA	нет данных n/a
Krishna-murthy S. [43]	2000	17	12 ГБМ 5 АА 12 GBM 5 AA	Гематопорфирин Hematoporphyrin	внутривенно intravenously	24 – 72	2	630	1500 – 5900	16,4 АА 3,8 ГБМ 16,4 AA 3,8 GBM	нет данных n/a
Stummer W. [33]	2007	1	ГБМ GBM	5-АЛК 5-ALA	перорально per os	24	20	633	1200	нет данных n/a	нет данных n/a
Beck T.J. [30]	2007	10	ГБМ GBM	5-АЛК 5-ALA	перорально per os	1	20	633	939 – 2304	15	нет данных n/a
Kaneko S. [44]	2008	20	16 ГБМ 4 АА 16 GBM 4 AA	Гематопорфирин Hematoporphyrin	внутривенно intravenously	24 – 48	2	630	180	20,5	нет данных n/a
Kaneko S. [44]	2011	26	18 ГБМ 6 АА 18 GBM 6 AA	Гематопорфирин Hematoporphyrin	внутривенно intravenously	24 – 48	2	630	180	15	нет данных n/a
Johans-son A. [16]	2013	5	ГБМ GBM	5-АЛК 5-ALA	перорально per os	5 – 8	20 – 30	635	720	3 и 9 (2), >29 (3)	>29 (3)
Schwartz C. [29]	2015	15	ГБМ GBM	5-АЛК 5-ALA	перорально per os	нет данных n/a	20 – 30	633	12960	34 – 37	16
Lietke S. [6]	2021	44	37 ГБМ 7 АА 37 GBM 7 AA	5-АЛК 5-ALA	перорально per os	3 – 5	20	635	5760 – 17 388	39,7	13

Quach S. [41]	2023	16	ГБМ GBM	5-АЛК 5-ALA	перорально per os	3	20	635	969 – 5760	28	16,4
Rafaelyan A.A. [26]	2023	10	7 ГБМ 3 АА 7 GBM 3 AA	5-АЛК 5-ALA	перорально per os	4	20	635	234 – 104	36,3	16,3
Rynda A.	2025	7	7 ГБМ 7 GBM	хлорин е6 chlorin e6	внутривенно intravenously	2	1	662	180	28,3	13,1

*ГБМ – глиобластома, ГС – глиосаркома, АА – анапластическая астроцитома, ОА – анапластическая олигодендроглиома, GP – первичная глиобластома, GR – рецидивная глиообластома.
*GBM – glioblastoma, GS – gliosarcoma, AA – anaplastic astrocytoma, OA – anaplastic oligodendroglioma, GP – primary glioblastoma, GR – recurrent glioblastoma.

According to the above criterion, it can be concluded that there is a lower proportion of local recurrences after iPDT compared with other treatments. However, no correlation was found between the distance of recurrence from the primary tumor and any other parameter evaluated. In our study, the median overall survival from the first diagnosis of malignant glioma to death was 28.3 months. The median recurrence-free survival was 13.1 months. Moreover, MGMT status played a significant role in the treatment outcomes of patients with iPDT.

Conclusion

In this study, we evaluated neuroimaging data, patient characteristics, and tumor molecular biological and cytogenetic data, which were collected and evaluated retrospectively. A thorough preoperative planning of the iPDT session was performed, taking into account multiple physical and biological parameters, using dedicated software. The MRI images obtained after iPDT were analyzed. In order to identify potential survival-related factors, various available parameters were examined for correlation with survival data. We also aimed to explore the potential of iPDT, and to motivate further research on this important topic and lay the foundation for future studies.

In conclusion, it should be noted that iPDT shows promising results regarding overall and relapse-free survival in the structure of complex treatment of patients with glioblastoma. At the same time, technical and clinical issues related to the small number of patients in the existing studies remain, which should be resolved in the future to determine the tactics of using iPDT and to develop a standard for the use of this technique in the treatment of malignant tumors of the central nervous system.

In the future, iPDT can also be combined with other treatment methods in order to be able to affect as many tumor cells as possible, with the initiation of a wide range of tissue and cellular processes that can help in the fight against this invasive tumor malignancy. To improve the control of tumor growth at a distance, a combination with immunotherapy or sonodynamic therapy may be of interest.

Interstitial PDT of gliomas remains a challenging procedure due to the limited depth of light penetration into the brain tissue, complex planning and implantation of the irradiator, and potential risk of clinical deterioration, especially after treatment in functionally important brain areas. However, iPDT may be a promising treatment option in a population of patients with a high risk of postoperative neurological deficit. It does not interfere with, but rather may complement, other treatment options for this disease, such as repeat radiotherapy and chemotherapy. iPDT remains a potential option for deep-seated gliomas in patients with high surgical risk and in case of tumor recurrence. Hospital stay with iPDT is significantly shorter, which reduces the cost of hospitalization. Patients treated with iPDT may receive adjuvant treatment more quickly than patients with standard craniotomy. These data strongly support further studies in controlled prospective settings.

REFERENCES

1. Louis D.N., Perry A., Wesseling P. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*, 2021, Vol.23(8), pp. 1231-1251. doi: 10.1093/neuonc/noab106.
2. Ostrom Q.T., Cioffi G., Waite K., et al. CBTRUS Statistical Report: primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014-2018. *Neuro Oncol*, 2021, Vol.23, pp. III1–III105. doi: 10.1093/NEUONC/NOAB200
3. Rynda A.Yu., Olyushin V.E., Rostovtsev D.M., et al. Intraoperative photodynamic therapy in complex treatment of malignant gliomas. *Zhurnal Voprosy Neirokhirurgii Imeni N.N. Burdenko*, 2023, Vol. 87(1), pp.25-34. (In Russian) doi:10.17116/neiro20238701125
4. Stepp H., Stummer W. 5-ALA in the management of malignant glioma. *Lasers Surg Med*, 2018, Vol.50, pp.399-419. doi: 10.1002/lsm.22933
5. Rynda A.Yu., Olyushin V.E., Rostovtsev D.M., et al. Intraoperative fluorescence control with chlorin E6 in resection of glial brain tumors. *Zhurnal Voprosy Neirokhirurgii Imeni N.N. Burdenko*, 2021, Vol.85(4), pp. 20-28. (In Russian). doi:10.17116/neiro20218504120

ЛИТЕРАТУРА

1. Louis D.N., Perry A., Wesseling P. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary // Neuro Oncol. – 2021. – Vol. 23(8). – P. 1231-1251. doi: 10.1093/neuonc/noab106.
2. Ostrom Q.T., Cioffi G., Waite K. et al. CBTRUS Statistical Report: primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014-2018 // Neuro Oncol. – 2021. – Vol. 23. – P. III1–III105. doi: 10.1093/NEUONC/NOAB200
3. Рында А.Ю., Олюшин В.Е., Ростовцев Д.М. и соавт. Применение интраоперационной фотодинамической терапии в структуре комплексного лечения злокачественных глиом // Журнал «Вопросы нейрохирургии» имени Н.Н. Бурденко – 2023. – Т. 87, №1. – С. 25-34. doi: 10.17116/neiro20238701125
4. Stepp H., Stummer W. 5-ALA in the management of malignant glioma // Lasers Surg Med. – 2018. – Vol. 50. – P. 399-419. doi: 10.1002/lsm.22933
5. Рында А.Ю., Олюшин В.Е., Ростовцев Д.М. и соавт. Результаты использования интраоперационного флюоресцентного контроля с хлорином Е6 при резекции глиальных опухолей головного мозга // Журнал «Вопросы нейрохирургии» имени Н.Н. Бурденко. – 2021. – Т. 85, №.4. – С. 20-28. doi: 10.17116/neiro20218504120.

6. Lietke S., Schmutzer M., Schwartz C. Interstitial Photodynamic Therapy Using 5-ALA for Malignant Glioma Recurrences. *Cancers (Basel)*, 2021, Vol.13(8), pp.1767. doi: 10.3390/cancers13081767
7. Rynda A.Y., Rostovthev D.M., Zabrodskaya Y.M. et al. Immunotherapy with autologous dendritic cells in the complex treatment of malignant gliomas – results. *J. Neurooncol*, 2024, Vol.166, pp.309-319. doi: 10.1007/s11060-023-04559-1
8. Foglar M., Aumiller M., Quach S., et al. Interstitial photodynamic therapy of glioblastoma: An MRI-based follow-up analysis. Photodiagnosis and Photodynamic Therapy., 2024, Vol.46, pp.104117. doi: 10.1016/j.pdpdt.2024.104117
9. Muller P.J., Wilson B.C. Photodynamic Therapy for Malignant Newly Diagnosed Supratentorial Gliomas. *J. Clin. Laser Med. Sur*, 1996, Vol.14, pp.263-270. doi: 10.1089/clm.1996.14.263
10. Rynda A.Y., Olyushin, V., Rostovtsev D. Immunotherapy With Autological Dendritic Cells in the Structure of Complex Treatment of Gliomas. *Neurosurgery*, 2024, vol.70 (Suppl.1), pp. 196. doi: 10.1227/neu.0000000000002809_1244
11. Foglar M., Aumiller M., Bochmann K. Interstitial Photodynamic Therapy of Glioblastomas: A Long-Term Follow-up Analysis of Survival and Volumetric MRI Data. *Cancers (Basel)*, 2023, Vol.15 (9), pp.2603. doi: 10.3390/cancers15092603
12. Romanishkin I.D., Savelieva T.A., Ospanov A. Comparison of optical-spectral characteristics of glioblastoma at intraoperative diagnosis and ex vivo optical biopsy. *Biomedical Photonics*, 2024, Vol.13(4), pp.4-12. doi:10.24931/2413-9432-2024-13-4-4-12
13. Rynda A.Yu., Rostovtsev D.M., Olyushin V.E. et al. Therapeutic pathomorphosis in malignant glioma tissues after photodynamic therapy with chlorin e6 (reports of two clinical cases). *Biomedical Photonics*, 2020, Vol.9(2), pp. 45-54. doi: 10.24931/2413-9432-2020-9-2-45-54
14. Ospanov A., Romanishkin I., Savelieva T., et al. Optical Differentiation of Brain Tumors Based on Raman Spectroscopy and Cluster Analysis Methods. *Int. J. Mol. Sci*, 2023, Vol.24, pp.14432. doi:10.3390/ijms241914432
15. Rynda A.Yu., Olyushin V.E., Rostovtsev D.M., et al. Comparative analysis of 5-ALA and chlorin E6 fluorescence-guided navigation in malignant glioma surgery. Pirogov Russian Journal of Surgery = Khirurgiya. *Zurnal im. N.I. Pirogova*, 2022, Vol.1, pp.5-14. (In Russian) doi: 10.17116/hirurgia20220115
16. Johansson A., Faber F., Kniebühler G., et al. Protoporphyrin IX fluorescence and photobleaching during interstitial photodynamic therapy of malignant gliomas for early treatment prognosis. *Laser Surg. Med*, 2013, Vol.45, pp.225-234. doi:10.1002/lsm.22126.
17. Savelieva T.A., Romanishkin I.D., Ospanov A., et al. Machine learning methods for spectrally-resolved imaging analysis in neuro-oncology. *Biomedical Photonics*, 2024, Vol.13(4), pp.40-54. doi: 10.24931/2413-9432-2024-13-4-40-54
18. Rynda A.Yu., Zabrodskaya Yu.M., Olyushin V.E., et al. Morphological evaluation of the effectiveness of fluorescence navigation with chlorin e6 in surgery for malignant gliomas. *Arkhiv Patologii*, 2021, Vol.83(5), pp.13-20. (In Russian) doi: 10.17116/patol20218305113
19. Henker C., Hiepel M.C., Kriesen T., et al. Volumetric assessment of glioblastoma and its predictive value for survival. *Acta Neurochir*, 2019, Vol.161, pp.1723-1732. doi: 10.1007/s00701-019-03966-6
20. Rynda A.Yu., Rostovtsev D.M., Olyushin V.E. Fluorescence-Guided Resection of Glioma – literature review. *Russian Neurosurgical Journal named after professor A.L. Polenov*, 2018, vol.X (1), pp.97-110. (In Russian)
21. Tzerkovsky D.A., Maslakov E.A., Bagrintsev D.A., Semak I.A., Protopovich Y.L., Chizh A.G., Tatur A.A., Fomenkov I.S., Stupak D.S. The role of photodynamic therapy in the treatment of primary, recurrent and metastatic malignant brain tumors. *Biomedical Photonics*, 2018, Vol.7(2), pp.37-49. (in Russian). doi: 10.24931/2413-9432-2018-7-2-37-49.
22. Rynda A.Yu., Olyushin V.E., Rostovtsev D.M., et al. Fluorescent diagnostics with chlorin e6 in surgery of low-grade glioma. *Biomedical Photonics*, 2021, Vol. 10(4), pp. 35-43 (in Russian). doi: 10.24931/2413-9432-2021-10-4-35-43
23. Kostron H., Hochleitner B.W., Obwegeser A., Seiwald M. Clinical and experimental results of photodynamic therapy in neurosurgery., 1994, pp.126-128. doi:10.1117/12.203437.
24. Potapov A.A., Chobulov S.A., Nikitin P.V., et al. Intraoperative vascular fluorescence in cerebral glioblastomas and vascular histological features. *Burdenko's Journal of Neurosurgery*, 2019, Vol.83(6), pp.21-34. (in Russian). doi: 10.17116/neiro20198306121
25. Rynda A.Yu., Rostovtsev D.M., Olyushin V.E., Zabrodskaya Yu.M. Fluorescence-guided resection of glioma using «photoditazin». *Grekov's Bulletin of Surgery*, 2017, Vol.176(5), pp.10-15. (In Russian). doi: 10.24884/0042-4625-2017-176-5-10-15
26. Rafaelian A., Martynov B., Chemodakova K., et al. Photodynamic interstitial stereotactic therapy for recurrent malignant glioma.

6. Lietke S., Schmutzer M., Schwartz C. Interstitial Photodynamic Therapy Using 5-ALA for Malignant Glioma Recurrences // Cancers (Basel). – 2021. – Vol.13(8). – P.1767. doi: 10.3390/cancers13081767
7. Rynda A.Y., Rostovthev D.M., Zabrodskaya Y.M. et al. Immunotherapy with autologous dendritic cells in the complex treatment of malignant gliomas – results // J. Neurooncol. – 2024. – Vol.166. – P. 309-319. doi: 10.1007/s11060-023-04559-1
8. Foglar M., Aumiller M., Quach S., et al. Interstitial photodynamic therapy of glioblastoma: An MRI-based follow-up analysis // Photodiagnosis and Photodynamic Therapy. – 2024. – Vol. 46. – P.104117. doi: 10.1016/j.pdpdt.2024.104117
9. Muller P.J., Wilson B.C. Photodynamic Therapy for Malignant Newly Diagnosed Supratentorial Gliomas // J. Clin. Laser Med. Sur. – 1996. – Vol.14. – P.263-270. doi: 10.1089/clm.1996.14.263
10. Rynda A.Y., Olyushin, V., Rostovtsev D. Immunotherapy With Autological Dendritic Cells in the Structure of Complex Treatment of Gliomas // Neurosurgery. – 2024. – Vol.70 (Suppl. 1). – P. 196. doi: 10.1227/neu.0000000000002809_1244
11. Foglar M., Aumiller M., Bochmann K. Interstitial Photodynamic Therapy of Glioblastomas: A Long-Term Follow-up Analysis of Survival and Volumetric MRI Data // Cancers (Basel). – 2023. – Vol. 15, (9). – P. 2603. doi: 10.3390/cancers15092603
12. Романишкин И.Д., Савельева Т.А., Оспанов А. и др. Сравнение оптико-спектральных характеристик глиобластомы при интраоперационной диагностике и оптической биопсии ex vivo // Biomedical Photonics. – 2024. – Т.13, №4. – С. 4-12. doi:10.24931/2413-9432-2024-13-4-4-12
13. Рында А.Ю., Ростовцев Д.М., Олюшин В.Е., Забродская Ю.М. Лечебный патоморфоз в тканях злокачественной глиомы после фотодинамической терапии с хлорином е6 (сообщение о двух клинических случаях) // Biomedical Photonics. – 2020. – Т. 9, №2. – С. 45-54. doi: 10.24931/2413-9432-2020-9-2-45-54
14. Ospanov A., Romanishkin I., Savelieva T., et al. Optical Differentiation of Brain Tumors Based on Raman Spectroscopy and Cluster Analysis Methods // Int. J. Mol. Sci. – 2023. – Vol. 24. – P. 14432. doi:10.3390/ijms241914432
15. Рында А.Ю., Олюшин В.Е., Ростовцев Д.М. и соавт. Сравнительный анализ флуоресцентной навигации в хирургии злокачественных глиом с использованием 5-АЛА и хлорина Е6 // Хирургия. Журнал им. Н.И. Пирогова. – 2022. – №1. – С. 5-14. doi: 10.17116/hirurgia20220115
16. Johansson A., Faber F., Kniebühler G., et al. Protoporphyrin IX fluorescence and photobleaching during interstitial photodynamic therapy of malignant gliomas for early treatment prognosis // Laser Surg. Med. – 2013. – Vol.45. – P.225-234. doi:10.1002/lsm.22126.
17. Савельева Т.А., Романишкин И.Д., Оспанов А. и др. Методы машинного обучения для анализа спектрально-разрешенных изображений в нейроонкологии. // Biomedical Photonics. – 2024. – Т.13, №4. – С. 40-54. doi:10.24931/2413-9432-2024-13-4-40-54
18. Рында А.Ю., Забродская Ю.М., Олюшин В.Е. и соавт. Морфологическая оценка эффективности флуоресцентной навигации с хлорином е6 в хирургии злокачественных глиом // Архив патологии. – 2021. – Т. 83, №5. – С.13-20. doi: 10.17116/patol20218305113
19. Henker C., Hiepel M.C., Kriesen T., et al. Volumetric assessment of glioblastoma and its predictive value for survival // Acta Neurochir. – 2019. – Vol.161. – P.1723-1732. doi: 10.1007/s00701-019-03966-6
20. Рында А.Ю., Ростовцев Д.М., Олюшин В.Е. Флуоресцентно-контролируемая резекция астроцитарных опухолей головного мозга – обзор литературы. // Российский нейрохирургический журнал имени профессора А.Л. Поленова. – 2018. – Т. X, №1. – С. 97-110.
21. Церковский Д.А., Маслаков Е.А., Багринцев Д.А., и др. Роль фотодинамической терапии в лечении первичных, рецидивных и метастатических злокачественных опухолей головного мозга // Biomedical Photonics. – 2018. – Т. 7, № 2. – С. 37-49. doi: 10.24931/2413–9432–2018–7–2–37–49
22. Рында А.Ю., Олюшин В.Е., Ростовцев Д.М. и соавт. Флуоресцентная диагностика с хлорином е6 в хирургии глиом низкой степени злокачественности // Biomedical Photonics. – 2021. – Т. 10, № 4. – С. 35-43. doi: 10.24931/2413–9432–2021–10-4-35-43
23. Kostron H., Hochleitner B.W., Obwegeser A., Seiwald M. Clinical and experimental results of photodynamic therapy in neurosurgery. – 1994. – P. 126-128. doi:10.1117/12.203437.
24. Потапов А.А., Чобулов С.А., Никитин П.В. и соавт. Интраоперационная флуоресценция сосудов в структуре глиобластом головного мозга и их гистологическая характеристика // Журнал «Вопросы нейрохирургии» имени Н.Н. Бурденко. – 2019. – Т.83, №6. – С.21-34. doi: 10.17116/neiro20198306121
25. Рында А.Ю., Ростовцев Д.М., Олюшин В.Е., Забродская Ю.М. Флюоресцентно-контролируемая резекция глиальных опухолей с «Фотодитазином» // Вестник хирургии имени И.И. Грекова. – 2017. – Т.176, №5. – С.10-15. doi: 10.24884/0042-4625-2017-176-5-10-15

Asian J Oncol, 2023, Vol.9, pp.14. doi:10.25259/ASJO-2022-69-(433)
27. Baran T.M., Foster T.H. Comparison of flat cleaved and cylindrical diffusing fibers as treatment sources for interstitial photodynamic therapy. *Med Phys*, 2014, Vol. 41, pp. 1-8. doi: 10.1118/1.4862078
28. Rynda A., Olyushin V., Rostovtsev D. Fluorescence navigation in glioma surgery using 5 ALA and chlorin E6. *Neuro-Oncology*, 2021, Vol. 23 (Suppl. 2), pp. ii25. doi: 10.1093/neuonc/noab180.086
29. Schwartz C., Rühm A., Tonn J.-C., Kreth S., Kreth F.-W. SURG-25 Interstitial photodynamic therapy of de-novo glioblastoma multiforme who iv. *Neuro-Oncol*, 2015, vol.17, pp. v219-v220. doi: 10.1093/neuonc/nov235.25
30. Beck T.J., Kreth F.W., Beyer W., et al. Interstitial photodynamic therapy of nonresectable malignant glioma recurrences using 5-aminolevulinic acid induced protoporphyrin IX. *Laser Surg. Med*, 2007, Vol.39, pp.386-393. doi:10.1002/lsm.20507.
31. Romanishkin I.D., Savelieva T.A., Ospanov A., et al. Classification of intracranial tumors based on optical-spectral analysis. *Biomedical Photonics*, 2023, Vol.12(3), pp.4-10. doi; 10.24931/2413-9432-2023-12-3-4-10
32. Rynda A.Yu., Olyushin V.E., Rostovtsev D.M., et al. Patients with long-term survival in malignant gliomas after photodynamic therapy. *S.S. Korsakov Journal of Neurology and Psychiatry*, 2024, Vol.124(6), pp.54-61. (In Russian). doi: 10.17116/jnevro202412406154
33. Stummer W., Beck T., Beyer W., et al. Long-sustaining response in a patient with non-resectable, distant recurrence of glioblastoma multiforme treated by interstitial photodynamic therapy using 5-ALA: case report. *J. Neuro-Oncol*, 2007, Vol.87, pp.103-109. doi:10.1007/s11060-007-9497-x
34. Rafaelian A.A., Martynov B.V., Chemodakova K.A. Stereotactic Photodynamic Therapy of Recurrent Malignant Gliomas. *Sovrem Tekhnologii Med*, 2024, Vol.16(2), pp.58-65. doi: 10.17691/stm2024.16.2.06
35. Muller P.J., Wilson B.C. Photodynamic therapy of malignant brain tumours. *Can. J. Neurol. Sci*, 1990, Vol.17 (2), pp.193-198. doi: 10.1017/s0317167100030444.
36. Rynda A.Yu., Olyushin V.E., Rostovtsev D.M., Zabrodskaya Yu.M., Papayan G.V. Results of microsurgical resection of glioblastomas under endoscopic and fluorescent control. *Biomedical Photonics*, 2024, Vol.13(3), pp.20-30. doi: 10.24931/2413-9432-2024-13-3-20-30
37. Origitano T.C., Reichman O.H. Photodynamic Therapy for Intracranial Neoplasms. *Neurosurgery*, 1993, vol. 32, pp. 587-596. doi:10.1227/00006123-199304000-00015.
38. Rynda A.Y., Olyushin V.E., Rostovtsev D.M. et al. Patients with Long-Term Survival in Malignant Gliomas after Photodynamic Therapy. *Neurosci Behav Physi*, 2024, Vol. 54, pp. 1215-1221. doi:10.1007/s11055-024-01717-4
39. Savelieva T., Romanishkin I. Ospanov A. Machine Learning and Artificial Intelligence Systems Based on the Optical Spectral Analysis in Neuro-Oncology. *Photonics*, 2025, vol.12(1), pp.37. doi: 10.3390/photonics12010037
40. Olyushin V.E., Kukanov K.K., Nechaeva A.S., Sklyar S.S., Vershinin A.E., Dikonenko M.V., Golikova A.S., Mansurov A.S., Safarov B.I., Rynda A.Y., Papayan G.V. Photodynamic therapy in neurooncology. *Biomedical Photonics*, 2023, Vol.12(3), pp.25-35. doi: 10.24931/2413-9432-2023-12-3-25-35
41. Quach S., Schwartz C., Aumiller M. et al. Interstitial photodynamic therapy for newly diagnosed glioblastoma. *J. Neurooncol*, 2023, Vol.162, pp.217-223. doi:10.1007/s11060-023-04284-9
42. Rafaelyan A.A., Alekseev D.E., Martynov B.V., et al. Stereotactic photodynamic therapy for recurrent glioblastoma. Case report and literature review. *Burdenko's Journal of Neurosurgery*, 2020, Vol.84(5), pp.81-88. (In Russian). doi: 10.17116/neiro20208405181
43. Krishnamurthy S., Powers S.K., Witmer P., Brown T. Optimal light dose for interstitial photodynamic therapy in treatment for malignant brain tumors. *Laser Surg. Med*, 2000, Vol.27, pp. 224-234. doi:10.1002/1096-9101(2000)27:3<224:aid-lsm4>3.0.co;2-#
44. Kaneko S. 悪性グリオーマに対する光線力学療法. *Nippon Laser Igakkaishi*, 2011, Vol. 32, pp.131-138. doi:10.2530/jslsm.32.131.
45. Powers S.K., Cush S.S., Walstad D.L., Kwock L. Stereotactic intratumoral photodynamic therapy for recurrent malignant brain tumors. *Neurosurgery*, 1991, Vol.29, pp. 688. doi:10.1097/00006123-199111000-00008.
46. Kostron H., Obwegeser A., Jakober R. Photodynamic therapy in neurosurgery: a review. *J. Photochem. Photobiol. B*, 1996, Vol.36(2), pp.157-168. doi: 10.1016/s1011-1344(96)07364-2
47. Ramakrishnan D., Reppert M., Krycia M. Evolution and implementation of radiographic response criteria in neuro-oncology. *Neuro-Oncology Advances*, 2023, Vol.5 (1), pp. vdad118. doi:10.1093/noajnl/vdad118
48. National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE); National Cancer Institute: Bethesda, MD, USA, 2017.

26. Rafaelian A., Martynov B., Chemodakova K., et al. Photodynamic interstitial stereotactic therapy for recurrent malignant glioma // Asian J Oncol. – 2023. – Vol.9. – P.14. doi:10.25259/ASJO-2022-69-(433)
27. Baran T.M., Foster T.H. Comparison of flat cleaved and cylindrical diffusing fibers as treatment sources for interstitial photodynamic therapy // Med Phys. – 2014. – Vol. 41. – P. 1-8. doi: 10.1118/1.4862078
28. Rynda A., Olyushin V., Rostovtsev D. Fluorescence navigation in glioma surgery using 5 ALA and chlorin E6. // Neuro-Oncology. – 2021. – Vol. 23 (Suppl. 2). – P. ii25. doi: 10.1093/neuonc/noab180.086
29. Schwartz C., Rühm A., Tonn J.-C., Kreth S., Kreth F.-W. SURG-25 Interstitial photodynamic therapy of de-novo glioblastoma multiforme who iv // Neuro-Oncol. – 2015. – Vol.17. – P. v219-v220. doi: 10.1093/neuonc/nov235.25
30. Beck T.J., Kreth F.W., Beyer W., et al. Interstitial photodynamic therapy of nonresectable malignant glioma recurrences using 5-aminolevulinic acid induced protoporphyrin IX // Laser Surg. Med. – 2007. – Vol.39. – P.386-393. doi:10.1002/lsm.20507.
31. Романишкин И.Д., Савельева Т.А., Оспанов А., и др. Классификация внутричерепных опухолей на основе оптико-спектрального анализа // Biomedical Photonics. – 2023. – Т.12, №3. – С. 4-10. doi: 10.24931/2413-9432-2023-12-3-4-10
32. Рында А.Ю., Олюшин В.Е., Ростовцев Д.М. и соавт. Пациенты с длительной выживаемостью при злокачественных глиомах после фотодинамической терапии // Журнал неврологии и психиатрии им. С.С. Корсакова. – 2024. – Т. 124, №6. – С. 54-61. doi: 10.17116/jnevro202412406154
33. Stummer W., Beck T., Beyer W., et al. Long-sustaining response in a patient with non-resectable, distant recurrence of glioblastoma multiforme treated by interstitial photodynamic therapy using 5-ALA: case report // J. Neuro-Oncol. – 2007. – Vol.87. – P. 103-109. doi:10.1007/s11060-007-9497-x
34. Рафаелян А.А., Мартынов Б.В., Чемодакова К.А., и др. Стереотаксическая фотодинамическая терапия рецидивных злокачественных глиом // Современные технологии в медицине. – 2024. – Т.16, №2. – С.58-67. doi: 10.17691/stm2024.16.2.06
35. Muller P.J., Wilson B.C. Photodynamic therapy of malignant brain tumours // Can. J. Neurol. Sci. – 1990. –Vol.17(2). – P.193-198. doi: 10.1017/s0317167100030444.
36. Рында А.Ю., Олюшин Д.М., Ростовцев Д.М., Забродская Ю.М., Папаян Г.В. Результаты микрохирургической резекции глиобластом под эндоскопическим и флуоресцентным контролем // Biomedical Photonics. – 2024. – Vol. 13(3). – P. 20-30. doi: 10.24931/2413-9432-2024-13-3-20-30
37. Origitano T.C., Reichman O.H. Photodynamic Therapy for Intracranial Neoplasms // Neurosurgery. – 1993. – Vol. 32. – P. 587-596. doi:10.1227/00006123-199304000-00015.
38. Rynda A.Y., Olyushin V.E., Rostovtsev D.M. et al. Patients with Long-Term Survival in Malignant Gliomas after Photodynamic Therapy // Neurosci Behav Physi. – 2024. – Vol. 54. – P. 1215-1221. doi: 10.1007/s11055-024-01717-4
39. Savelieva T., Romanishkin I. Ospanov A. Machine Learning and Artificial Intelligence Systems Based on the Optical Spectral Analysis in Neuro-Oncology // Photonics. – 2025. – Vol.12(1). – P.37. doi: 10.3390/photonics12010037
40. Олюшин В.Е., Куканов К.К., Нечаева А.С., и др. Фотодинамическая терапия в нейроонкологии // Biomedical Photonics. – 2023. – Vol.12(3). – P.25-35. doi: 10.24931/2413-9432-2023-12-3-25-35
41. Quach S., Schwartz C., Aumiller M. et al. Interstitial photodynamic therapy for newly diagnosed glioblastoma // J. Neurooncol. – 2023. – Vol.162. – P.217-223. doi:10.1007/s11060-023-04284-9
42. Рафаелян А.А., Алексеев Д.Е., Мартынов Б.В., и др. Стереотаксическая фотодинамическая терапия в лечении рецидива глиобластомы. Случай из практики и обзор литературы // Журнал «Вопросы нейрохирургии» имени Н.Н. Бурденко. – 2020. – Vol. 84(5). – P.81-88. doi: 10.17116/neiro20208405181
43. Krishnamurthy S., Powers S.K., Witmer P., Brown T. Optimal light dose for interstitial photodynamic therapy in treatment for malignant brain tumors. // Laser Surg. Med. – 2000. – Vol.27. – P. 224-234. doi:10.1002/1096-9101(2000)27:3<224:aid-lsm4>3.0.co;2-#
44. Kaneko S. 悪性グリオーマに対する光線力学療法 // Nippon Laser Igakkaishi. – 2011. – Vol. 32. – P.131-138. doi:10.2530/jslsm.32.131.
45. Powers S.K., Cush S.S., Walstad D.L., Kwock L. Stereotactic intratumoral photodynamic therapy for recurrent malignant brain tumors // Neurosurgery. – 1991. – Vol.29. – P. 688. doi:10.1097/00006123-199111000-00008.
46. Kostron H., Obwegeser A., Jakober R. Photodynamic therapy in neurosurgery: a review // J. Photochem. Photobiol. B. – 1996. – Vol.36(2). – P.157-168. doi: 10.1016/s1011-1344(96)07364-2
47. Ramakrishnan D., Reppert M., Krycia M. Evolution and implementation of radiographic response criteria in neuro-oncology // Neuro-Oncology Advances. – 2023. – Vol.5 (1). – P. vdad118. doi:10.1093/noajnl/vdad118
48. National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE); National Cancer Institute: Bethesda, MD, USA. – 2017.