MODERN POSSIBILITIES OF TREATING BRAIN TUMORS: INTRAOPERATIVE TECHNOLOGIES IN NEUROONCOLOGY

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ABSTRACT

The fundamental principle of neurooncology is the maximal removal of the tumor, simultaneously minimizing the effects on the healthy brain structures. In cases of malignant gliomas, the extent of resection still remains a critical parameter, which significantly affects the prognosis of the disease. The results from numerous trials show that the increase of the resected tumor volume correlates with improved survival rates. This review provides the data on the innovative intraoperative therapeutic technologies, developed for improving the treatment outcomes among the patients with brain tumors. It is important to note that each of these technologies has its benefits and limitations. For example, laser interstitial thermotherapy provides the ability of highly precise destruction of tumor cells with minimal damaging of the surrounding healthy tissues, however, it requires special equipment and qualified personnel. Photodynamic therapy is distinguished by selective affecting the tumor, but its efficiency depends on the type of photosensibilizing agent used and on the depth of light penetration. Brachytherapy, in turn, provides the possibility of local tumor irradiation, minimizing the effects on the surrounding structures, but it can require a long-term following up the patient after the procedure. Thus, the use of modern intraoperative methods gives access to new perspectives in neurooncology, providing a more precise and sparing destruction of tumors with preserving the functional activity of the healthy brain structures. However, the success of their use depends on further development of technologies, on increasing the qualification of specialists and on the close interactions of the scientific community with the industry and with the regulating authorities.

Keywords: *neurosurgery; oncology; technologies; laser interstitial thermal ablation; photodynamic therapy; brachytherapy; innovations; glioma; glioblastoma.*

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INTRODUCTION

The fundamental principle of neurooncology is to maximally resect the tumor, simultaneously minimizing the effects on the healthy structures of the brain. In cases of high-grade gliomas (HGG), the extent of resection still remains a critical parameter, which significantly affects the prognosis of the disease. Numerous research works show that the increase of the volume of resected tumor correlates with improved survival rates [1–3]. However, it is important to take into account that the excessively aggressive surgical approach can result in the development of new neurological disorders in a patient, which, in turn, can negatively affect the overall survival, especially concerning the tumors, located in the functionally important areas of the brain [4]. Even despite the progress in the surgical techniques, the risk of recurrences remains high due to the presence of residual infiltrative cells at the border of the tumor and beyond its margins. This determines the necessity of constant searching and implementing new intraoperative technologies, capable of increasing the precision of tumor visualization and providing

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СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ ЛЕЧЕНИЯ НОВООБРАЗОВАНИЙ ГОЛОВНОГО МОЗГА: ИНТРАОПЕРАЦИОННЫЕ ТЕХНОЛОГИИ В НЕЙРООНКОЛОГИИ

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АННОТАЦИЯ

Основополагающий принцип нейроонкологии заключается в том, чтобы максимально удалить опухоль, одновременно минимизировав воздействие на здоровые структуры головного мозга. В случае злокачественных глиом объём резекции продолжает оставаться критическим параметром, который существенно влияет на прогноз болезни. Результаты многочисленных исследований показывают, что увеличение объёма удалённой опухоли коррелирует с улучшенными показателями выживаемости. В данном обзоре представлены инновационные интраоперационные терапевтические технологии, созданные для улучшения исходов лечения пациентов с опухолями головного мозга. Важно отметить, что каждая из этих технологий имеет свои преимущества и ограничения. Например, лазерная интерстициальная термотерапия обеспечивает высокоточную деструкцию опухолевых клеток с минимальным повреждением окружающих здоровых тканей, однако требует специального оборудования и квалифицированного персонала. Фотодинамическая терапия отличается избирательным воздействием на опухоль, но её эффективность зависит от типа используемого фотосенсибилизатора и глубины проникновения света. Брахитерапия, в свою очередь, предоставляет возможность локального облучения опухоли, минимизируя воздействие на окружающие структуры, но может требовать длительного периода наблюдения за пациентом после процедуры. Таким образом, применение современных интраоперационных методов открывает новые перспективы в нейроонкологии, обеспечивая более точную и щадящую деструкцию опухолей при сохранении функциональной активности здоровых структур мозга. Однако успех их применения зависит от дальнейшего развития технологий, повышения квалификации специалистов и тесного взаимодействия научного сообщества, индустрии и регуляторов.

Ключевые слова: *нейрохирургия; онкология; технологии; лазерная интерстициальная термоабляция; фотодинамическая терапия; брахитерапия; инновации; глиома; глиобластома.*

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the possibility of detecting and eliminating the microscopically small remnants of the tumor cells along the margins of the post-operative cavity after the main stage of resecting the tumor. Due to that, special importance is gained by modern methods of intraoperative diagnostics, such as the fluorescent navigation, the spectroscopy and the molecular visualization, which allow the surgeon to better navigate at the operative field and to more precisely determine the margins between the healthy tissues and the tumor. These approaches promote to decreasing the risk of damaging the healthy tissues and to increasing

the radicality of the surgical intervention, which can potentially improve the remote treatment results.

For the purpose of preventing the continued growth of HGG cells, actively invading the normal nerve tissue, the exclusive importance is being gained by the methods of intraoperative therapy, such as the laser interstitial thermotherapy, the intraoperative brachytherapy, the photodynamic and the sonodynamic therapy.

The analysis of modern literature performed in this article, has allowed for characterizing the novel technologies of intraoperative therapy, to examine their current status and to evaluate the clinical results of their use in neurooncology.

Methodology of searching the trials

The search in the PubMed, Google Scholar and eLibrary electronic data bases was carried out in Russian and English languages using the following key words and their combinations: «neurosurgery»; «oncology»; «gliomas»; «glioblastoma»; «laser interstitial thermoablation»; «photodynamic therapy»; «brachytherapy».

The algorithm of selecting the sources consisted of several stages (Fig. 1). During the process of screening, the review authors have independently analyzed the titles and the abstracts of the selected articles, checking their conformity to the review topic; then, full-text manuscripts were assessed for the conformity to the inclusion criteria (publication in Russian or English languages; the article is a literature review or a clinical trial; the article is published in the peer-reviewed scientific journal; the article describes the use of intraoperative technologies in neurooncology). Ultimately, the present review has enlisted 63 research works.

LASER INTERSTITIAL THERMOTHERAPY

Laser interstitial thermotherapy (LITT) is a minimally invasive ablation method, employing the thermal energy for destroying the tumor tissue [5]. The procedure is being undertaken at the stereotaxic manner, usually under the control of magnetic resonance tomography and under general anesthesia. For the introduction of the optical fiber, a small opening is created, through which, the low-energy laser radiation is being delivered for a period of 3–4 hours [6]. The heat created during this procedure destroys the blood-brain barrier, for a certain time period (up to 4–6 weeks after the procedure) improving the penetration of the medicinal products [7]. The immunomediated death of tumor

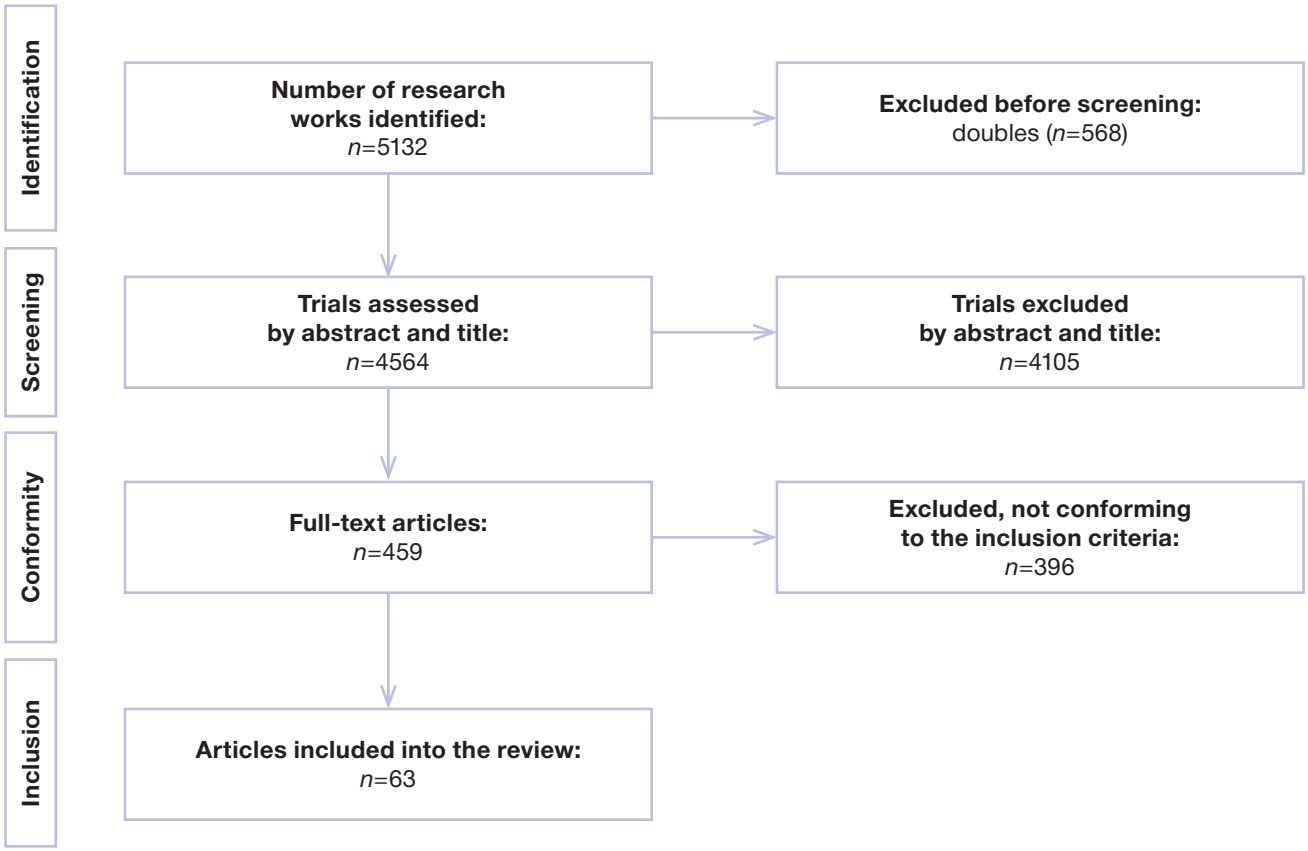

Fig. 1. Algorithm of searching the research works.

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cells, induced by LITT hyperthermia, in combination with the immunotherapy, can contribute to overcoming the blood-brain barrier and stimulating the cellular anti-tumor immune response, in particular, due to using the inhibitors of immune checkpoints [7, 8]. At the present moment, only the first phase of the trial is completed, with the research work being devoted to the combined use of LITT and monoclonal antibodies against the programmed death-ligand 1 (PD-L1) — the Avelumab, additional research is expected [9, 10].

As of today, two LITT systems are being actively used — the NeuroBlate (predominantly in neurooncology) and the Visualase (more often used for the treatment of drug-resistant epilepsy) [11–13]. Both devices can be used in accordance with various indications.

The NeuroBlate system, approved in 2009 by the Food and Drug Administration of the USA (FDA), is a controlled magnetic resonance device for performing the LITT procedures, employing laser hyperthermia for the purpose of *in situ* local heating the targets [14]. The first phase of clinical trials with the participation of patients suffering from the recurrent HGG, was arranged in 2013 in a group of 10 patients, the mean survival of which was 10.5 months [15]. The LAANTERN (Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System; NCT02392078) trial is a large research work supported by Monteris, during which, for a period of 5 years beginning from 2015, a total of 3000 patients were enlisted from various medical centers. One of the first to examine the efficiency of LITT in cases of newly diagnosed and recurrent wild type glioblastoma were the researchers J.F. de Groot et al. [16]. According to the results of their trial that included 29 patients with newly diagnosed and 60 patients with recurrent tumor, the median of overall survival among the patients with the newly diagnosed disease was comparable to the results observed in cases of standard surgical resection. Also, data were published on the treatment efficiency for metastatic lesions in the brain and for epilepsy [17, 18]. Besides, NeuroBlate is being tested within the framework of the randomized REMASTER controlled trial (REcurrent Brain Metastases After SRS Trial; NCT05124912), studying the brain metastases, as well as within the PENSAR (NCT05075850) international trial devoted to evaluating the neuropsychological outcomes, the results of which demonstrate the mean overall survival of 16.4 months and the relapse-free survival of 11.93 months. The median survival rate after using the LITT was almost 9 months, while in case of surgical resection this parameter has varied within a range of 5–13 months, which confirms the efficiency of minimally invasive alternative traditional surgery in case of newly diagnosed and recurrent IDH-positive glioblastomas with a short recovery period and lower risk of adverse effects.

The Visualase System approved by the FDA in 2008, was initially developed for the treatment of drug-resistant temporal epilepsy and since then it became a subject for numerous research works [19, 20]. Current trials, such as the SLATE, evaluate the safety and efficiency of Visualase in the treatment of mesial temporal epilepsy [21]; research works are being undertaken on the application of Visualase in the treatment of brain tumors [22, 23]. Thus, P.R. Jethwa et al. [22] have reported about a case series with the participation of 20 patients with brain tumors, 17 of which have previously used other types of therapy. The authors have noted that all the procedures have allowed for achieving a high precision of laser exposure (83.8%), and the majority of patients could leave the hospital already on the next day after surgery.

Despite the fact that direct comparisons between the NeuroBlate and the Visualase systems are lacking, both of them are demonstrating positive results and are being studied in the on-going clinical trials.

INTRAOPERATIVE BRACHYTHERAPY

Intraoperative brachytherapy represents a method of introducing radioactive materials directly into the tumor zone or near it before local radiation therapy. This approach can be used both inside the cavities of the organism and in the inter-tissue spaces [24]. Due to the directed effects of high radiation dosages on the tumor with minimal damaging the adjacent healthy tissues, the treatment efficiency gets increased [25].

Initially, brachytherapy was developed as an additional method of fighting malignant tumors in the abdominal cavity organs, but, at the modern level of technology, it is widely used in the treatment of various types of tumors, including the neoplasms in the central nervous system, in the prostate, in the mammary gland, in the female reproductive organs and in the eyes [26–29]. There are two main types of brachytherapy — the high-dose rate (HDR) and the low-dose rate (LDR).

During the HDR, the radiation source is being introduced into the tumor area for a short period of time (several minutes), being extracted afterwards. In case of the LDR, the radioactive material is left at the affected zone at least for several days, as a maximum —

for long (permanent) time [30]. After the main surgical intervention, into the resulting cavity, the radioactive isotope granules are commonly being placed, such as Cesium-131 (Cs-131), Iodine-125 (I-125) and Iridium-192 (Ir-192), the half-life of which ranges from several days to several weeks [31, 32].

In a number of clinical research works, the confirmation was obtained for the safety and efficiency of using brachytherapy for the treatment of brain tumors. Thus, S.T. Magill et al. [32] have used I-125 brachytherapy in 42 patients with atypical or recurrent meningiomas. The results have demonstrated that the mean duration of the recurrence-free period was 20.9 months for atypical and 3.3 years for recurrent meningiomas. E. Dagnew et al. [33] have observed similar findings in the research with the participation of 26 patients with brain metastases, where the local tumor control was reaching 96%, while the median of overall survival was 17.8 months. However, both research works have reported complications associated with the necrosis of the brain tissue due to radiation-induced damage, which, probably, was related to high initial dosage of I-125, characterized by relatively high disintegration energy (35 keV) and by the long half-life (59.4 days) [31]. This is why Cs-131, having an optimal ratio of energy (30 keV) and the half-life (9.7 days), has become the most preferable radioactive isotope for low-dose brachytherapy.

In the phase I/II clinical research conducted by A.G. Wernicke et al. [34], the procedures of permanent implantation of Cs-131 granules were performed in 24 patients with newly diagnosed metastases in the brain. One year later, the authors have observed 93.8% of local tumor control with no serious adverse effects related to radiation exposure. Similar results of controlled toxicity were also obtained during the other phase I/II trial with the participation of 15 patients [35].

After the successful use of Cs-131 in the low-dose mode of brachytherapy, the Gammatile (USA) device was made, representing the Cs-131 granules embedded into a collagen carrier, which is intended for the intracavitary implantation after surgery. The efficiency of this device was verified during the STaRT trial (Surgically Targeted Radiation Therapy), which has enlisted 11 patients with 16 HGG tumor foci (12 recurrent and 4 treatment-naive) [36]. The use of Gammatile has provided the local remission of 83% tumors within 12 months, while among the treatment-naive tumor cases this parameter was 100%. Currently, there is a ROADS phase III clinical trial going on, comparing the results of using Gammatile with the results of post-operative stereotactic radiosurgery (SRS). The completion of this research is planned for 2027 [37].

Among the recent advances in onco-radiology, it is important to note the Xoft Electronic Brachytherapy intraoperative balloon electronic brachytherapy systems (Axent, USA), which deliver the miniature source of X-ray radiation directly to the bed of the tumor, avoiding the necessity of using radioactive isotopes and the cost intensive equipment [25]. The radiation sources are being delivered via the applicator devices, providing a high dose of radiation to the surrounding tissues. The Intrabeam system by Zeiss (Germany) works as a miniature linear accelerator, creating a high-dose radiation for immediate radiation therapy after surgery with a minimal exposure of healthy tissues. A multicenter research by M. Huss et al. [38] with the use of these systems has demonstrated an improvement of overall survival by 25% in 3 years after the intervention.

The Xoft Axxent system (iCAD), equipped with a compact X-ray tube and a tungsten target, is showing high precision and safety of its radiation. Its ability to rapidly decrease the dosage helps minimizing the effects of radiation in the surrounding healthy tissues, with is especially valuable when operating in the vulnerable areas, such as the brain. Initially developed for the treatment of mammary gland and skin cancer, the Axxent system, due to its flexible software, can generate the dosage rate that is comparable with such radioactive isotopes as Ir-192, with no additional regulatory or logistical difficulties related to the usage of radioactive materials [39].

The Elekta Esteya (Sweden) is also an effective electronic solution for brachytherapy, initially developed for the treatment of non-melanoma skin cancers, but later extended for using during the intraoperative treatment of HGG due to its compact construction and its advanced capabilities of regulating the dosage rates. Using the 69.5 kV voltage, the Esteya system is capable of providing high power when using the low-energy X-ray beam, which increases its safety both for the patients and for the medical staff. The design of the Esteya system allows for conducting a precisely directed treatment, minimizing the radiation exposure to the non-targeted areas, making it attractive for using in neurooncology [39].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) represents a treatment method which combines using the light source and the non-toxic photosensibilizing agents for destroying the tumor cells [40]. The light is pointed directly at the

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tumor via the optical fibers, located inside or within the cavity forming after resecting the tumor [41]. Under the effects of the light with a specific wavelength and intensity, the photosensibilizing agent becomes activated, then producing the active oxygen species [7, 42]. These compounds react with the cellular components, causing the free-radical-induced death of tumor cells [42]. Currently, the most widely used photosensibilizing agent for PDT in cases of HGG is the 5-Aminolevulinic acid (5-ALA) [7, 43] — the precursor of the photoactive porphyrins (the fluorescent agent and simultaneously the source of active oxygen species) in the tumor tissues. The PDT-combined fluorescent navigation, mediated by 5-ALA, has become the object of multiple current clinical trials.

The efficiency of PDT, to a significant extent, is due to the selective accumulation of photosensibilizing agents in the malignant tumor cells, which is related to their ability to bind to the low density lipoproteins — the important components of the cellular membrane [42, 44]. As a result, the tumor cells, which rapidly reproduce and have high biosynthetic demands, devour the low density lipoproteins and the photosensibilizing agents at a much higher rate comparing to the healthy cells.

The anti-tumor effects of PDT are diverse. Besides the direct destruction of tumor cells by means of oxidative damage, PDT also causes ischemia in the tumor, damaging its vascular network and suppressing the formation of new blood vessels [45]. Besides, PDT stimulates both the innate and the adaptive immune reactions, which uncovers the interesting perspectives for clinical trials [45].

Hemerion (France) has developed a photosensibilizing agent named Pentalafen and the Heliance device, which are being introduced into the tumor before surgery and intraoperationally [46]. The aim of the INDYGO (INtraoperative photoDYnamic Therapy for GliOblastomas; NCT03048240) staged clinical research conducted at the facilities of the Lille University Hospital, was the evaluation of safety and efficiency of the intraoperative 5-ALA-mediated PDT after a fluorescent navigation surgery [47]. The research included only 10 patients with newly diagnosed HGG during a period from May 2017 until June 2018 [47]. Upon the completion of the research in April 2021, the provisional analysis of the results did not show any significant adverse effects, while the overall survival and the progression-free survival rates for a period of 12 months were 60% and 80%, respectively [48]. The next stage of the INDYGO research is the DOSINDYGO (Dose Finding for Intraoperative Photodynamic Therapy of Glioblastoma; NCT04391062) trial — a multicenter phase II clinical trial on determining the maximal tolerable dose of 5-ALA-mediated PDT [49]. Currently, an active recruitment of participants is still going on, the completion of the research is planned for September 2025.

The research by A.Yu. Rynda et al. [50] has assessed the efficiency of intraoperative PDT in patients with HGG of supratentorial location (n=161). The patient cohort was divided into the main group receiving PDT (n=80) and the comparison group without PDT (n=81). The usage of intraoperative technologies within the structure of the combined treatment for malignant gliomas has significantly increased the median overall survival in Grade III patients to 39.1±5.5 months, in Grade IV patients — up to 20.7±4.7 months, also increasing the inter-recurrent period. No serious complications were observed that were related to the use of the photosensibilizing agent.

Thus, the application of the intraoperative PDT within the structure of the combined treatment for malignant gliomas promotes to an increase in the overall survival and in the inter-recurrent period, making this method a perspective direction in neurooncology.

SONODYNAMIC THERAPY AND FOCUSED ULTRASOUND

Sonodynamic therapy (SDT) represents an alternative method of treatment, which employs a non-toxic sonosensitizing compound together with focused ultrasound exposure for destroying the tumor cells [51]. The focused ultrasound transfers acoustic energy via the ultrasonic transducer into the target tissue areas with high spatial precision. Just like PDT, the sensitizer is mainly concentrated in the tumor cells, which allows for performing a targeted ablation. The basic mechanism of action of the focused ultrasound includes the formation of the cavitation effect (from the Latin cavitas — the emptiness), during which, the induction of ultrasonic waves results in a series of alternating cycles of high and low pressure, causing the formation and further implosion (a type of explosion) of microbubbles with heating the surrounding tissues [51]. The microbubbles mechanically disrupt the blood-brain barrier, temporarily increasing its permeability, which facilitates the localized delivery of medicines [52].

Currently, there are two leading companies that work on the development of the technologies related to the use of focused ultrasound for impairing the integrity of the blood-brain barrier in the treatment of gliomas:

InSightec Ltd. (Israel) has developed an improved system of focused ultrasound exposure under the magnetic resonance tomography control, and CarThera (France) has developed a SonoCloud low-intensive contact ultrasonic system. During the phase I clinical research, which had recruited 17 recurrent glioblastoma patients, A.M. Sonabend et al. [53] have demonstrated the safety and efficiency of the transient impairment of the blood-brain barrier permeability using the SonoCloud device, as well as an improved delivery of albumin-bound Paclitaxel and Carboplatin through the blood-brain barrier. One of the most studied SDT sensitizers is the same 5-ALA compound. Currently, SonALAsense (USA) is conducting a single-center phase 0 clinical trial with an evaluation of safety and efficiency of increased SDT dosage rates combined with 5-ALA (SONALA-001) in the treatment of HGG (NCT04559685).

Such technologies as SDT and focused ultrasound, offer innovative solutions for the treatment of tumors that are hard to access. The usage of non-toxic compounds and ultrasound for targeted destruction of tumor cells represents a promising strategy, which will help improving the treatment results and lowering the risk of adverse effects. It is important to continue the research and development in this field to optimize the existing treatment methods and to increase their efficiency.

THE MODERN FOCUS OF SCIENTIFIC DEVELOPMENT

The entirety of the novel intraoperative treatment methods indicates the significant progress in the neurosurgery of brain tumors, offering specialized instruments for overcoming the high recurrence rate and for solving the complex issues of HGG therapy. Such methods as the LITT, PDT and SDT, focused ultrasound and brachytherapy, demonstrate a synergetic effect comparing to classic resection, promoting to the preservation of a large extent of healthy tissue and to the improvement in the quality of life for the patients. In parallel with such physical effects, local chemotherapeutic approaches are being developed that ensure the maximal efficiency directly in the lesion focus. For example, Carmustine (Bischlorethylnitrosourea, BCNU), an alkylating agent (the nitrosourea derivative) that was initially used for the treatment of gliomas by means of intravenous injection and that was later introduced (in the form of biodegradable plates containing Carmustine (Gliadel)) into the cavity remaining after removing the tumor [54]. The plate format, intended for decreasing the systemic toxicity, simultaneously ensures the localized exposure at the margins of the resection area [54]. In the meta-analysis conducted by L. Zhao et al. [55], the combination of surgical resection of tumor with the introduction of Carmustine plates has prolonged the overall survival in patients with newly diagnosed multiform glioblastomas for 2–4 months. Nevertheless, despite the positive results, the usage of Carmustine plates, for a number of reasons, has not yet become the standard treatment of glioblastomas, including due to the significant technical difficulty of the procedure. In addition to that, in the meta-analysis by A. Bregy et al. [56], the rate of complications observed when using the Carmustine plates, was exceeding the value of 42% (most commonly — seizures and cerebral edema), even taking into consideration the observed decrease in the number of systemic adverse effects for the plate form of Carmustine. Additional barriers for wide implementation of Carmustine plates include the high costs and the logistical difficulties of using the method in the settings of the operating room.

The modern focus of scientific development is aimed predominantly at the HGG, which represent a serious problem due to their high occurrence rates, the resistance to the existing treatment methods and the unfavorable prognosis. The survival rates remain extremely low, despite many years of research and the progress in technologies [57]. The two key biological features of HGG — the heterogeneity of the tumor and its ability to spread outside the contrasted zone — require a combined integration of various technologies and therapeutic strategies [58]. As of today, the combinations of various high-tech methods are used, such as surgery with fluorescent control and the exoscopy and Raman spectroscopy combined with LITT, PDT, SDT and focused ultrasound exposure. These methods are combined with the immunotherapy with checkpoint inhibitors and with the conventional chemoradiation therapy. For the purpose of further perfecting the therapy, more precise *in vitro* and *in vivo* models are required, which are capable of reproducing the heterogeneous origin of HGG [59, 60]. The limited representation of the existing pre-clinical models complicates the course of translational trials [60]. Besides the biological challenges related to the heterogeneity of tumors, it must be kept in mind that the implementation of new technologies in surgery is inevitably accompanied by an increase of costs and of the duration of training for specialists.

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There is a topical need for increasing the number of phase 0 and I clinical research works. As noted by the STARD-CNS recommendations [61], special attention must be paid to the possible mistakes when designing the trials, especially concerning the new fluorophores. These early research stages are critically important for the evaluation of safety, applicability and preliminary efficiency of new technologies, opening the path for more large-scaled testing of the promising treatment methods at the next stages. The important aspect of the wide implementation of new methods of intraoperative diagnostics and therapy is obtaining the approval for clinical application from the regulatory authorities (for example, FDA), which itself is a long-term and complex process. Due to that, the experience of registering Gliolan, a medicinal product that is based on 5-ALA, can represent a valuable lesson [62]. Within the framework of this process, the 5-ALA was approved by the FDA, which allowed the researchers to repurpose its use from therapy to the intraoperative visualization tool. This example demonstrates the significance of flexibility and innovativeness in the process of transitioning the laboratory science innovations into clinical practice.

CONCLUSION

The active development of new technologies and treatment methods in neurooncology represents a remarkable example of human inventiveness for increasing the efficiency of treating the poorly curable gliomas of high degree of malignancy. Each of the intraoperative therapeutic technologies described in the review, contributes greatly into the improvement of the treatment outcomes for patients with brain tumors. Thus, LITT provides the precise elimination of the tumor cells, minimally affecting the adjacent healthy tissues, however, this procedure requires specialized equipment and experienced specialists. PDT directly affects the tumor, but the efficiency of the method is determined by the type of photosensibilizing agent used and by the depth of penetration of the activating light beam. Brachytherapy, in turn, allows for performing local irradiation of the tumor, limiting the effects in the surrounding areas, nevertheless, after this procedure, the patient may require a long-term follow-up period.

The cooperation between the scientific community, the industry and the regulating authorities can play a key role in the successful implementation of the reviewed technological innovations into clinical practice.

ADDITIONAL INFORMATION

Author contribution. *A.I. Nafikov*, *R.I. Minnigaleev* — concept and design of the study, editing of the article; *E.R. Yarullina* — collection and analysis of literary sources, preparation and writing of the text of the article; *E.M. Magomedova* — collection and analysis of literary sources, preparation and writing of the text of the article; *K.G. Soboleva* — literature review, collection and analysis of literary sources, writing the text and editing the article; *M.M. Sobolev* — search and analysis of literature, writing the text of the article; *O.R. Egamova*, *Yu.A. Kirillova*, *A.A. Harutyunyan* — data collection and analysis, editing the manuscript; *E.M. Magomedova* — data collection and analysis, participation in the writing of the manuscript; *K.G. Soboleva*, *F.A. Tokhova*, *N.A. Abbasova*, *Kh.Kh. Saadueva*, *I.F. Yarmeev* — data collection and analysis, writing the text of the manuscript. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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