DOI: 10.21294/1814-4861-2025-24-6-138-148
УДК: 616-006.494-08:578.7



Для цитирования: *Венглер Д.С., Кулигина Е.В., Васильева Н.С., Рихтер В.А., Чернышова А.Л., Тамкович С.Н.* Препараты на основе онколитических вирусов как перспективные средства для лечения глиобластомы. Сибирский онкологический журнал. 2025; 24(6): 138–148. – doi: 10.21294/1814-4861-2025-24-6-138-148
For citation: *Vengler D.E., Kuligina E.V., Vasileva N.S., Richter V.A., Chernyshova A.L., Tamkovich S.N.* Oncolytic viruses as promising agents for treating glioblastoma. Siberian Journal of Oncology. 2025; 24(6): 138–148. – doi: 10.21294/1814-4861-2025-24-6-138-148

# ONCOLYTIC VIRUSES AS PROMISING AGENTS FOR TREATING GLIOBLASTOMA

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**Abstract**

**Background.** Glioblastoma is a highly aggressive, difficult-to-treat brain cancer with a poor prognosis, high mortality, and a significant impact on quality of life. Despite decades of research, standard treatments can extend life, but do not cure the disease, making it a focus for new research in neuro-oncology, immunotherapy, targeted therapy, and personalized medicine. The disease affects people of working age (with peak incidence between 45 and 70 years of age), causing damage to families and society. High costs of treatment and palliative care exacerbate the problem. **The purpose of the study** was to summarize data on modern approaches to the treatment of glioblastoma and to analyze efficacy and side effects of oncolytic virus therapy. **Material and Methods.** The literature review of studies published over the past 10 years was conducted using PubMed, eLIBRARY, Springer, Google Scholar, etc. databases. **Results.** Modern glioma therapy uses a multidisciplinary approach combining surgery, chemotherapy, and radiation therapy. Oncolytic virotherapy for brain glioma is a promising field because it uses viruses to selectively target to cancer cells while also stimulating an immune response against the tumor. Current research confirms that oncolytic therapy is effective against a variety of tumors including those that are resistant to traditional treatments. Clinical studies show that virotherapy can be a safe treatment because viruses are often engineered to be selective for cancer cells like glioma, minimizing damage to healthy tissue, although questions remain about optimizing dosage and overcoming the immune response. **Conclusion.** Oncolytic virotherapy is a highly promising approach for the treatment of glioblastoma. Oncolytic viruses are currently in various stages of research, and have promise in animal models, with the potential to lead to new personalized treatments for solid tumors.

**Key words: glioblastoma, virotherapy, oncolytic virus for the treatment of glioblastoma, vaccinia virus, recurrent glioblastoma, modern approaches to the treatment of glioblastoma.**

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# ПРЕПАРАТЫ НА ОСНОВЕ ОНКОЛИТИЧЕСКИХ ВИРУСОВ КАК ПЕРСПЕКТИВНЫЕ СРЕДСТВА ДЛЯ ЛЕЧЕНИЯ ГЛИОБЛАСТОМЫ

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**Аннотация**

**Введение.** Актуальность исследований глиобластомы обусловлена ее высокой агрессивностью, почти 100 % смертностью, отсутствием эффективного лечения и катастрофическим воздействием на качество жизни пациентов. Несмотря на десятилетия исследований, стандартная терапия лишь незначительно продлевает жизнь, но не излечивает болезнь. Это делает глиобластому областью поиска прорывных научных решений в нейроонкологии, иммунотерапии, таргетной терапии и персонализированной медицине. Заболевание поражает людей трудоспособного возраста (с пиком заболеваемости между 45 и 70 годами), нанося социальный ущерб. Высокая стоимость лечения и паллиативной помощи усугубляет проблему. **Цель исследования –** обобщить и систематизировать данные о современных подходах к лечению глиобластомы. Провести анализ данных по терапевтическим и побочным эффектам онколитических вирусов. **Материал и методы.** С помощью электронных ресурсов поисковых систем PubMed, eLIBRARY, Springer, Google Scholar и др. проведен обзор литературы, содержащей доказательные экспериментальные и клинические данные по обсуждаемым вопросам, за последние 10 лет. **Результаты.** Современные подходы к лечению глиом включают хирургическое лечение, химиотерапию и лучевую терапию. Разработанная в настоящее время виротерапия глиом головного мозга, сочетающая в себе высокую специфичность к опухолевым клеткам и способность стимулировать противоопухолевый иммунный ответ, представляется чрезвычайно перспективной. Современные исследования демонстрируют эффективность онколитической терапии против различных типов опухолей, в том числе резистентных к традиционным методам лечения. Безопасность виротерапии подтверждена клиническими исследованиями: большинство вирусов избирательно воздействуют на клетки глиомы, что сводит к минимуму повреждение здоровых тканей. Однако остаются вопросы по оптимизации дозировок онколитических вирусных препаратов и преодолению противовирусного иммунного ответа. Кроме того, разрабатываются методы доставки вирусов к опухолям. **Заключение.** Терапия глиобластомы с помощью онколитических вирусов считается одним из наиболее перспективных методов лечения. В настоящее время онколитические вирусы проходят различные стадии исследований, причем многие из них показывают многообещающие результаты на животных моделях. Дальнейшие исследования в этой области могут привести к созданию новых персонализированных методов лечения, улучшающих прогноз для пациентов с солидными опухолями.

**Ключевые слова: глиобластома, виротерапия, онколитический вирус для лечения глиобластомы, вирус коровьей оспы, рецидивирующая глиобластома, современные подходы к лечению глиобластомы.**

Gliomas are the most common (80–85 %) primary brain tumors in adults. The incidence of gliomas is comparable across European countries, the US, and Russia, with rates of 6 cases per 100,000 people in Europe [1], 7 cases per 100,000 in the US [2], and 6 cases per 100,000 in Russia [3]. Over the past 20 years, the incidence of gliomas has shown a slight increase globally, primarily due to improved diagnostic tools like MRI, immunohistochemical testing, etc., and secondarily, due to the aging of the population [4]. The five-year survival rate for patients with gliomas ranges from 5 % to 90 %. This indicator is influenced by the type of glioma, as well as timely diagnosis and the patient's region of residence (five-year survival rates are higher in large cities) [4].

Gliomas can affect people of all ages, and represent a significant socioeconomic burden. The direct costs of glioma treatment are the medical expenses, which include neuroimaging, doctor and specialist visits, surgery, and hospital stays. Indirect costs are the non-medical expenses, such as patient transportation, specialized nutrition, home nursing care, and personal

Table/Таблица

**Classification of gliomas [9]**
**Классификация глиом [9]**

| | |
|---|---|
| Gliomas, glio-neuronal and neuronal tumors/ Глиомы, глио-нейрональные и нейрональные опухоли | Astrocytic tumors, IDH-mutant (diffuse astrocytomas, glioblastoma)/ Астроцитарные опухоли, IDH-мутантные (диффузные астроцитомы, глиобластома) |
| | Astrocytic tumors, IDH-wild type (glioblastoma, IDH-wild type)/ Астроцитарные опухоли, IDH-дикий тип (глиобластома, IDH-дикий тип) |
| | Oligodendrogliomas, IDH-mutant and 1p/19q codeleted/ Олигодендроглиомы, IDH-мутантные и мутантные по 1p/19q |
| | Ependymal tumors/ Эпендимальные опухоли |
| | Other gliomas (e.g., choroid plexus tumors)/ Другие глиомы (например, опухоли хороидального сплетения) |
| | Glioneuronal and neuronal tumors (ganglioglioma, dysembryoplastic neuroepithelial tumor)/ Глионейрональные и нейрональные опухоли (ганглиоглиома, дизэмбриопластическая нейроэпителиальная опухоль) |

Примечание: таблица составлена авторами.

Note: created by the authors.

hygiene products. A survey conducted by the National Brain Tumor Foundation in 2006 showed that 91 % of brain tumor patients were working before their diagnosis, compared to 33 % after their diagnosis. Among those who cared for patients, 16 % stopped working, and 62 % reduced their working hours or took leave. Forty-eight percent of respondents reported a decrease in family income, and families as a whole reported a reduction in spending [5, 6]. Accordingly, even among stable, highly functional patients who survived glioma, financial burden and disability were prevalent across all subtypes, treatment regimens, and family income levels.

The symptoms of gliomas depend on which part of the central nervous system (CNS) is affected. Depending on its location, a glioma can cause headaches, vomiting, memory loss, seizures, vision problems, aphasia, and cranial nerve dysfunction. Vision loss in patients with glioma is caused by a tumor in or around the optic nerve. Spinal cord gliomas can cause pain, weakness, or numbness in the limbs by compressing the spinal nerve roots. Gliomas do not usually metastasize through the bloodstream, but they can spread through the cerebrospinal fluid [7]. Complex visual hallucinations have been described as a symptom of low-grade glioma [8].

Gliomas are classified according to the type of precursor cells: astrocytomas (diffuse, anaplastic, glioblastoma), oligodendrogliomas, ependymomas), and the grade of malignancy (grade 1 is benign, slow-growing glioma (e.g., pilocytic astrocytoma, and grade 4 is highly aggressive, with infiltrative growth (e.g., glioblastoma)) (Table) [9]. In the 5th edition of the World Health Organization (WHO) classification of central nervous system tumors, specific molecular changes were included in the classification of gliomas. The updated WHO classification, based on histology and molecular changes, has provided a better understanding of the clinical, radiological, molecular, survival, and prognostic characteristics of different glioma subtypes, as well as providing precise recommendations for diagnosis and potential prognosis for patients.

### Glioblastoma is the most common and aggressive type of glioma

The incidence of glioblastoma, the most common malignant primary brain tumor in adults (45–54 % of all gliomas), is 3–4 cases per 100,000 per year, increasing after the age of 40 and peaking between the ages of 75 and 84 [10]. Other types of gliomas characterized by lower malignancy (astrocytomas, oligodendrogliomas) usually affect patients under the age of 50 [11]. It has been shown that glioblastoma is more common in Caucasians than in other ethnic groups [12]. The five-year survival rate for patients with glioblastoma is approximately 5 %, making this tumor one of the most dangerous types of brain cancer [13].

### Modern approaches to glioma therapy

There are a number of difficulties in treating gliomas: verifying the type of tumor, taking into account the heterogeneous molecular profile of the tumor; selecting the appropriate therapy; the patient's response to the chosen treatment method; achieving sustained remission; and others. In view of the above, the development of approaches to personalized therapy for gliomas is an extremely urgent task for molecular oncology. Modern methods of treating gliomas depend on the type of tumor. Below are universal approaches to treating this CNS malignancy.

#### *Surgical treatment*

This type of treatment is used to remove as much of the tumor as possible in order to improve neurological functions, most often using minimally invasive microsurgical techniques. In addition, surgical resection of the tumor allows for histological examination, on the basis of which targeted therapy can be selected. To prevent iatrogenic postoperative neurological com-

plications, navigation systems are used during tumor removal surgery: intraoperative MRI, ultrasound, PET CT, and others [14]. The use of evoked potentials, electromyography, or mapping in awake patients under local anesthesia to monitor and preserve speech and cognitive abilities allows tumor resection in areas of the cortex responsible for these functions. Preventing new irreversible neurological disorders during surgery is more important than the extent of resection, since gliomas cannot be completely cured by surgery due to their growth characteristics [14].

***Radiation therapy***

This type of therapy is used in patients with gliomas to prevent recurrence after surgery. The indications for treatment, timing, dosage, and schedule of radiation therapy are determined by the diagnosis and prognostic factors [14]. Despite the improved prognosis for the course of the disease, radiation therapy has a number of side effects. In particular, this therapy may cause damage to the optic nerves, optic chiasm, retina, lenses, brain stem, pituitary gland, cochlea, and hippocampus [15]. The use of modern radiation therapy methods, such as stereotactic or intensity-modulated radiation therapy, helps to reduce the number of negative effects of radiation exposure by limiting the area of exposure and/or selecting the site of exposure more accurately [14, 15].

***Chemotherapy***

First-line chemotherapy treatment for newly diagnosed glioma, regardless of tumor morphology, includes temozolomide (TMZ). The presumed mechanism of action is based on the ability of its metabolites to methylate guanine bases in DNA. After oral administration, the prodrug temozolomide is absorbed in the small intestine and, due to its small size, crosses the blood-brain barrier. After entering the cell, temozolomide undergoes spontaneous hydrolysis, converting into the potent methylating agent 3-methyl-(triazen-1-yl) imidazole-4-carboxamide (MTIC). MTIC methylates a number of nucleosides, primarily guanine, leading to apurinization and further breaks in the deoxyribose phosphate backbone, which in turn triggers apoptosis [15].

To increase the effectiveness of temozolomide, the principle of chronotherapy is applied, since the level of expression of genes responsible for cell replication, genes affecting metabolic rate, and genes responsible for DNA repair fluctuate throughout the day in accordance with the circadian rhythm and are regulated by the suprachiasmatic nucleus of the hypothalamus, whose activity depends on light levels [16]. It is known that BMAL1 gene expression in tumor cells is subject to circadian rhythms [17]. Temozolomide-induced apoptosis of tumor cells is enhanced during peak BMAL1 expression and appears to consistently reach a maximum approximately 5 hours after dusk [18]. Accordingly, accurate calculation of the timing of temozolomide administration in accordance with its pharmacokinetic characteristics allows maximum therapeutic effect to be achieved by deactivating DNA repair mechanisms in tumor cells.

It should be noted that temozolomide therapy may be ineffective due to the varying sensitivity of glioma cells to this drug. Low sensitivity to temozolomide, caused by demethylation of the MGMT gene promoter, whose product is responsible for DNA repair during methylation, is estimated at 10–15 % in the case of demethylated MGMT to 40–50 % in other cases in terms of five-year survival rate [19].

In this regard, it is necessary to search for new methods of postoperative treatment for patients who do not respond to temozolomide [20, 21]. In addition, like most cytostatic drugs, temozolomide has a number of side effects, the most common of which are nausea, myelosuppression (manifested by thrombocytopenia and neutropenia), alopecia, and myoclonic seizures [22]. The vast majority of patients experience recurrence of glioma after therapy [23, 24]. Lomustine, carmustine (alkylating derivatives of nitrosourea), and temozolomide are used to treat recurrence, but their effectiveness is low [25].

An alternative chemotherapy method for treating recurrent glioblastoma is the PCV therapeutic regimen, based on a combination of procarbazine, lomustine, and vincristine. Vincristine belongs to a group of alkaloids obtained from the flowering plant periwinkle. Vincristine binds to tubulin and inhibits microtubule formation, which leads to disruption of spindle formation and arrest of mitosis. In addition, vincristine inhibits protein and nucleic acid synthesis by blocking the use of glutamic acid [26, 27]. The PCV regimen combined with radiation therapy provides an antitumor effect, but has pronounced neurotoxicity that exceeds the neurotoxicity of each component individually [28]. In addition, the drugs included in the PCV regimen are hepatotoxic, and their effect on the nervous system is not limited to the central nervous system – various polyneuropathies have been noted among the side effects, including dysfunction of the cranial nerves, causing paresis of the eyes and vocal cords, depriving the person of the ability to see and speak normally. Accordingly, this therapy is often used as palliative care when other methods are ineffective, as it significantly reduces the patient's quality of life [29–31].

***Antiangiogenic Therapy***

Bevacizumab is a recombinant hyperchimeric humanized IgG1 monoclonal antibody that binds to and inhibits vascular endothelial growth factor, leading to a reduction in tumor vascularization. Bevacizumab is approved for the treatment of gliomas both in combination with temozolamide and radiation therapy and as monotherapy [32]. In addition, this drug may be used in combination with irinotecan, a topoisomerase 1 inhibitor [33]. Inhibition of topoisomerase 1 in cells slows down DNA replication processes, leading to

reduced production of various agents, including vascular endothelial growth factor. Thus, the combination of bevacizumab and irinotecan enhances the effect of the drugs [32–34]. Limiting angiogenesis in the tumor slows down the growth of CNS tumors, but in the case of gliomas, it does not completely stop tumor development. A number of side effects of bevacizumab, including increased blood pressure, rectal bleeding, and gastric and intestinal ulcers, limit the use of this drug [34].

***Alternative therapeutic approaches***

Due to the low efficacy of standard treatment regimens for gliomas and glioblastomas in particular, new therapeutic methods and approaches are currently being developed and implemented. Local delivery methods are aimed at delivering therapeutic agents directly to the tumor, bypassing the blood-brain barrier, which allows for maximum concentration of the drug in the tumor while minimizing possible systemic side effects. Laser interstitial thermotherapy is the selective ablation of a lesion or tissue using heat emitted by a laser device. This method is considered less invasive than open surgery and is a solution for patients who cannot undergo surgical intervention. Stereotactic injections are also used to treat brain tumors. The procedure involves injecting an antineoplastic drug directly into the tumor. An analogue of stereotactic injections is the intra-arterial delivery system – this method reduces the invasiveness of the procedure, as it does not require trepanation of the skull, and the drug is delivered to the tumor through arterial access.

Convection-enhanced delivery is a method of delivering drugs in which a pressure gradient is created at the tip of the catheter so that substances are delivered to the brain by volumetric flow rather than diffusion. To perform the procedure, catheters are inserted into the interstitial space of the brain through holes drilled in the skull under imaging guidance. The catheters are connected to an infusion pump, which is used to create a volumetric flow pressure gradient. At an infusion rate of 0.1–10 μl/min, the drug enters the interstitial space, displacing extracellular fluid.

Implantable reservoirs allow continuous administration of the drug into the tumor over a long period of time. Currently, the only local drug delivery method approved by the Food and Drug Administration (FDA) for the treatment of glioblastoma is the Gliadel (Gliadel) – biodegradable copolymers (prolifeprosan 20) impregnated with the alkylating agent carmustine. This plate, containing 7.7 mg of carmustine, is placed in the surgical field immediately after tumor removal, with the number of plates determined individually in each case and depending on the size of the tumor and the surgical field. Within 2–3 weeks, the plates dissolve and the gradually released active substance acts on the remaining malignant cells. A serious disadvantage of the Gliadel plate is its rigid structure, which can lead to trauma to the soft tissues of the brain [35, 36].

Thus, the lack of a therapeutic strategy that would allow for a complete cure of glioblastoma is associated with both the molecular characteristics of the tumor and the individual response of patients to chemotherapy drugs. The drugs developed and used in the treatment of glioblastoma slightly increase the patient's life expectancy, but both the drugs themselves and the methods of their delivery to the CNS are associated with a high risk of side effects, which may limit the use of therapy. The question of the ratio of efficacy to the severity of side effects from the drugs used remains open, which requires the search for new methods of CNS glioma therapy.

**Virotherapy – the latest trend in immunotherapy for cancer**

Tumor virotherapy is currently an approved cancer treatment method based on the use of genetically modified or natural oncolytic viruses to selectively destroy tumor cells. Virotherapy is considered a promising approach, especially for the treatment of brain tumors (e.g., glioblastoma), where traditional methods are often ineffective [37]. It has been shown that cancer patients experienced tumor shrinkage or regression when infected with certain viruses [38]. Although oncolytic viruses are potentially powerful therapeutic agents for the treatment of CNS tumors, a single type of oncolytic virus is not sufficient to destroy all oncotransformed cells due to the heterogeneity of tumor tissues and tumor heterogeneity.

Among the factors limiting the effectiveness of virotherapy, the following can be highlighted: the ability of tumors to evade the immune response even when it is additionally induced by the spread of viral particles; the viscosity of the extracellular matrix, which can affect the spread of viral particles from cell to cell; the production of virus-neutralizing antibodies, which reduce the effectiveness of virotherapy with repeated injections [39].

To overcome these limitations, oncolytic viruses can be used in combination with other anticancer drugs and therapeutic approaches, whose shortcomings, in turn, can be compensated for by virotherapy [39]. Accordingly, the current tasks of virotherapy are to select the right type of virus that will be effective for a specific type of tumor, as well as a method of delivering the viral agent to the tumor that, on the one hand, will induce a virus-mediated antitumor immune response, but at the same time will not pose a danger to the weakened immune system of a cancer patient [40].

**Virotherapy for glioblastoma**

In 2021, the oncolytic virus G47Δ (Delytact Injection) was approved in Japan for the treatment of residual or recurrent glioblastoma [41]. G47Δ is a third-generation recombinant herpes simplex virus strain in which the γ34.5 gene has been deleted to eliminate the neurotoxicity of the virus, and 312 bp of

the α47 gene has been deleted to improve virus replication and reproductive capacity, as well as to enhance its antitumor activity. Insertion of the ECOL-I LacZ gene into the ICP6 region led to the inactivation of nucleotide reductase, which ensured the ability of the virus to replicate only in tumor cells, thereby improving its safety profile and increasing its tropism for tumor cells [41, 42]. G47Δ demonstrated high replication capacity in various cancer cells, effectively induced specific antitumor immunity, and showed a high level of infectious safety [42]. During Phase II of the clinical trial, each patient with recurrent glioma received stereotactic injections of G47Δ into the tumor every 4 weeks for a total of 6 injections. An interim analysis of the clinical trial data showed that the one-year survival rate of the 13 patients participating in the trial was 92.3 %. Serious side effects associated with G47Δ were observed in only 2 patients – high fever [43]. Later studies showed that one-year survival was 84.2 %, and median overall survival and progression-free survival were 20.2 months and 4.7 months, respectively, after starting G47Δ, which sets it apart from other treatments [44]. According to pooled data from 16 studies of various chemotherapeutic drugs for the treatment of recurrent glioblastoma, the median overall survival is 5.0 months, and the median progression-free survival is 1.8 months [45]. Unfortunately, the oncolytic virus G47Δ is not effective in all types of gliomas, which is associated with the high histochemical heterogeneity of the tumor. In this regard, the search for new variants of oncolytic viruses that improve the prognosis for glioma is a very urgent task in molecular oncology.

Newcastle disease virus (NDV) is an oncolytic virus that selectively replicates in tumor cells without affecting normal cells. NDV causes cancer cell death through mechanisms such as apoptosis, autophagy, and necroptosis, and can also stimulate an antitumor immune response by releasing cytokines and chemokines that attract immune cells to the tumor site. This feature makes NDV a promising candidate for oncolytic virotherapy of CNS tumors, including glioblastoma [46]. A limitation in the use of this virus for glioblastoma therapy is the absence of a mutation in the CDKN2A gene, which is responsible for the ability of tumor cells to synthesize type 1 interferon. To predict the effectiveness of NDV virotherapy for glioblastoma, tumor genotyping is used, which is an expensive procedure that is not always available to patients [47].

ZIKV is a mosquito-borne flavivirus belonging to the flavivirus genus, *Flaviviridae* family, which includes multiple important human pathogens such as dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV), and hepatitis C virus (HCV). ZIKV has an 11-kb positive-stranded RNA genome with positive polarity that encodes three structural proteins and seven nonstructural proteins [45]. The Zika virus primarily affects neural stem cells and neural progenitor cells (NPCs), leading to cell cycle arrest, apoptosis, and differentiation suppression, which has serious consequences for the brain [44]. Infection with the Zika virus in adults is usually asymptomatic or causes only mild symptoms, such as a slight fever and rash, which resolve on their own within about 7 days. Glial stem cells are the main cause of drug resistance and recurrence of malignant glioma [48]. The tropism of the Zika virus for glial stem cells makes it a very promising oncolytic vector that can destroy glial stem cells and prevent tumor recurrence, whereas other oncolytic vectors for the treatment of malignant glioma do not show a preference for glial stem cells [49]. However, the main problems with the clinical application of the Zika virus are safety and stability. It has been proven that a live attenuated vaccine candidate containing a 10-nucleotide deletion in the 3'-untranslated region (Δ10 3'-UTR) of the ZIKV-FSS13025 strain, has good oncolytic activity and is safe for BALB/c nude mice in which human glial cells were grown [50]. Normal brain cells are almost unaffected in immunocompetent mice treated with the Δ10 3′-UTR of the ZIKV-Dakar strain [51]. Although ZIKV demonstrated a good safety profile in treating mice with glioma, safety requires further consideration in clinical application.

rQNestin34.5v.2 is an oncolytic herpes simplex virus 1 (oHSV) that retains expression of the neurovirulent ICP34.5 gene under glioma-selective transcriptional regulation. ICP34.5 allows HSV1 to survive interferon and improves viral replication by dephosphorylation of the eIF-2α translation factor. rQNestin34.5v.2 dephosphorylated eIF-2α in human glioma cells, but not in human normal cells, resulting in significantly higher cytotoxicity and viral replication in the former compared to the latter [52]. Oncolytic herpes simplex virus type 1 (oHSV) has been one of the most widely studied OVs: one type of oHSV has been FDA approved for the treatment of melanoma [53]. rQNestin34.5v.2 was cytotoxic to all glioma cells, reducing cell survival to less than 20 % of the control. On the other hand, no significant cytotoxicity was detected in normal human and mouse cells: more than 80 % of cells survived after 72 hours of incubation. rQNestin34.5v.2 replicates in much larger quantities and has a more cytotoxic effect on glioma cells compared to normal cells [52].

The measles virus, belonging to the *Paramyxoviridae* family, is a single-stranded RNA virus with negative polarity. The effectiveness of the measles virus against glioma stem cells has been demonstrated *in vivo* and *in vitro*. MV-CEA is derived from the Edmonston strain, an attenuated strain used to vaccinate humans against measles, and expresses carcinoembryonic antigen (CEA) to detect viral gene expression [54]. MV-CEA, which exhibits antitumor activity through the interaction of fusion proteins and hemagglutinin, which have a high affinity for overexpressed CD46 receptors on glioblastoma cells. This treatment option was tested in a single study published on ClinicalTrials.gov. According to the researchers,

the group of patients who received an injection of this virus into the tumor bed showed a slight increase in life expectancy [55].

Parvovirus is a single-stranded DNA virus belonging to the *Parvoviridae family*. H-1PV is a rat protoparvovirus that is non-pathogenic to humans and has a cytotoxic effect, causing DNA damage and cell cycle arrest [56]. In one Phase I/IIa study, no safety concerns were identified with intravenous or intratumoral administration of H-1PV to patients with recurrent glioblastoma followed by tumor resection and re-administration of the drug into the resection cavity. In addition, evidence of viral spread within the tumor and associated immune activation was obtained. One patient experienced progressive deterioration 2 days after treatment, and imaging results indicated hydrocephalus. Surgical intervention did not reveal increased intracranial pressure, and it was not possible to establish a clear etiology or direct link to the treatment. The patient did not regain consciousness after 6 months and died after being taken off life support [57].

DNX2401, an oncolytic adenovirus that selectively targets tumors, has shown promising results in Phase I clinical trials. Published data indicate that the median overall survival of patients with glioblastoma receiving DNX2401 was 9.5 months. It is important to note that 20 % of these patients lived for more than 3 years after treatment, indicating a positive and long-term effect in some patients. In addition, after treatment with DNX2401, signs of inflammation and necrosis were observed in the tumor area [58]. Histopathological analysis revealed infiltration of CD8+ T cells and T-bet+ cells. This indicates that DNX-2401 not only causes tumor regression through direct oncolysis, but also triggers an antitumor immune response [59].

Toca 511, another potential treatment, is a retrovirus carrying the cytosine deaminase gene. This virus can selectively replicate in tumor cells, producing cytosine deaminase. The cytidine deaminase enzyme, encoded by the Toca 511 gene, converts the prodrug 5-fluorocytosine (5-FC) into the active chemotherapeutic drug 5-fluorouracil (5-FU) [60]. This enzymatic process enables targeted chemotherapy within the tumor, minimizing the potential systemic toxicity associated with 5-FU. In an earlier study of glioblastoma patients receiving Toca 511 therapy, the median overall survival was 14.4 months. In addition, five cases of complete remission were observed [61].

PVSRIPO, or PVS-RIPO, is the name of a modified polio virus that has recently shown promise for treating cancer. PVS-RIPO consists of a genetically modified nonpathogenic version of the oral poliovirus Sabin type 1. The internal ribosome entry site (IRES) on the poliovirus was replaced with the IRES from human rhinovirus type 2 (HRV2), to avoid neurovirulence. Once administered, the virus enters and begins replicating within cells that express CD155/Necl5, which is an onco-fetal cell adhesion molecule that is common across solid tumors. PVS-RIPO has shown promising results in the treatment of recurrent glioblastoma: median overall survival was 24 months [62]. PVS-RIPO uses a dual approach to directly destroy cancer cells and simultaneously trigger an immune response in the patient. These two mechanisms of action are closely linked at both the mechanical and biological levels, as evidenced by the immunostimulatory process of ICD. ICD is a non-canonical form of cell death caused by viruses, which promotes an immune response against antigens present in dead cells. This process involves apoptosis accompanied by the release of adenosine triphosphate, the pro-inflammatory cytokine high-mobility group box 1, and calreticulin. These released molecules immediately attract dendritic cells, present antigens to cytotoxic T lymphocytes, and activate gamma-delta T cells, which leads to a stronger effect on tumor cells [63].

VV-GMCSF-Lact is a recombinant strain developed on the basis of the L-IVP strain of the vaccinia virus. The genome of this virus is represented by double-stranded DNA, which replicates exclusively in the cytoplasm, eliminating the risk of its integration into the human genome [64]. The mechanism of oncolytic action of the vaccinia virus has not been fully studied. In general, caspase-dependent apoptosis is a universal mechanism of cellular defense against viruses and other intracellular pathogens, including the vaccinia virus, which prevents the accumulation of the virus and its transmission to neighboring cells [65]. In addition, infection with the vaccinia virus also causes programmed necrosis [66]. The combination of these two mechanisms of cell death makes the vaccinia virus one of the main candidates for the development of oncolytic virotherapy agents based on it [67]. VV-GMCSF-Lact contains deletions of viral thymidine kinase and growth factor gene fragments, into which the genes for human granulocyte-macrophage colony-stimulating factor and the apoptosis-inducing protein lactapin have been inserted [68]. Human GM-CSF induces a local antitumor immune response by attracting granulocytes and macrophages, and stimulates dendritic cell differentiation [69]. Lactaptin is a proteolytic fragment of human milk kappa-casein that has oncotoxic activity against tumor cells, causing their apoptosis via the mitochondrial pathway [70]. Currently, the VV-GMCSF-Lact virus has successfully completed Phase I clinical trials as a treatment for breast cancer, including triple-negative subtypes. In addition, *in vivo* experiments on various animal models have demonstrated the antitumor efficacy of this virus against human and animal glial tumors, both as monotherapy and in combination with temozolomide. It has been shown that the most effective treatment regimen for glioblastoma is VV-GMCSF-Lact virotherapy followed by temozolomide chemotherapy after 8 days [71, 72].

It has been shown that the simultaneous use of virotherapy and chemotherapy, probably due to the heterogeneity of glial tumors, has a less pronounced therapeutic effect. Indeed, after administration, the vaccinia virus promotes the activation of cytoplasmic

ATR kinase [73], which is one of the key enzymes in the induction of DNA repair [74]. Accordingly, the simultaneous administration of the oncolytic virus VV-GMCSF-Lact with temozolomide reduces the effectiveness of the latter by increasing the reparative functions of the cell with respect to methylated MTIC DNA, i.e., by enhancing the mechanisms of glioma cell resistance to this drug [74].

Since infection of multiple tumor cells with VV-GMCSF-Lact causes massive virus replication, the resulting tissue lysis triggers poorly controlled inflammation in the confined space of the skull. To reduce the side effects of virotherapy, it is most preferable to administer VV-GMCSF-Lact directly into the tumor bed after resection [75]. In this case, the virus will replicate in the remaining tumor cells, improving the results of surgical treatment.

Thus, therapy with oncolytic viruses is a promising tool in oncology, combining effectiveness and relative safety. At the same time, the development of new treatments and the modification of existing ones are complicated by the following factors: the low incidence of gliomas limits the size of patient groups that could participate in evaluating the effectiveness of new treatments; chemotherapy or radiation therapy is always preceded by surgery, the purpose of which is to remove the tumor conglomerate. However, after surgery, many patients show rapid deterioration, which prevents them from continuing treatment in the first days after surgery, when therapy can have the maximum effect [76].

## Conclusion

Current approaches to glioma treatment include surgery, chemotherapy, and radiation therapy. Oncolytic virotherapy is a promising new strategy that uses viruses to selectively destroy tumor cells and stimulate an antitumor immune response. Current research demonstrates the effectiveness of oncolytic therapy against various types of tumors, including those resistant to traditional treatments.. Clinical studies show that virotherapy can be a safe treatment because viruses are often engineered to be selective for cancer cells like glioma, minimizing damage to healthy tissue, although questions remain about optimizing dosage and overcoming the immune response. Further studies are required to develop new personalized treatments for solid tumors.

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Поступила/Received 27.09.2025
Одобрена после рецензирования/Revised 25.11.2025
Принята к публикации/Accepted 08.12.2025

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All authors approved the final version of the article prior to publication and agreed to take responsibility for all aspects of the work, including proper investigation and resolution of issues related to the accuracy and integrity of any part of the work.

***Funding***

*The study was supported by the grant No. 24-14-00390 from the Russian Science Foundation (https://rscf.ru/en/project/24-14-00390/).*

***Conflict of interests***

*The authors declare that they have no conflict of interest.*

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***Финансирование***

*Исследование выполнено при поддержке гранта Российского научного фонда № 24-14-00390 (https://rscf.ru/en/project/24-14-00390/).*

***Конфликт интересов***

*Авторы заявляют об отсутствии конфликта интересов.*