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Efficacy of oncolytic viruses (OVs) in malignant tumor therapy: a review on its therapeutic aspects

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Received 12 February 2026, Revised 17 April 2026, Accepted 18 April 2026, Available online 21 April 2026, Version of Record 4 May 2026.

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Highlights

- Dual-pronged mechanism of action - Oncolytic viruses (OVs) operate through a dual mechanism: direct and selective cytolysis of cancer and then induction of systemic anti-tumor immunity by releasing TAA and danger signals.
- Genetic engineering for enhanced selectivity - Advanced genetic modifications, such as deletion of the TK gene or usage of promoters that are tumor-specific, allowing the OVs to exploit the metabolic vulnerabilities and defective antiviral pathways that are distinctive to cancer cells.
- Transformation of the tumor microenvironment - OVs act as immunotherapy primers that has the ability to convert immunologically cold tumors into hot zones by recruitment of T-cells and upregulation of immune checkpoint signals like PD-L1.
- Synergistic combination therapies - Clinical evidence have demonstrated that the oncolytic viruses have significantly enhanced the efficacy of conventional oncotherapy and contemporary immunotherapies, achieving significant objective response rates of up to 62% when paired with immune checkpoint inhibitors like Pembrolizumab.

Abstract

Despite the life-saving potential of mainstream cancer therapies like surgery, chemotherapy and radiation, the clinical effectiveness is often limited by systemic toxicity, a lack of specificity and the survival of resistant cancer stem cells. With a global cancer burden projected to exceed over 30 million new cases by 2050, oncolytic virotherapy has emerged as a significant development in cancer treatment. These viruses - either natural or genetically modified, selectively infect the cancer cells, replicate within them and destroy while sparing the healthy tissue. This review examines the therapeutic effectiveness and biological mechanisms of oncolytic viruses (OVs) as a modern approach to treating cancer aiming to discuss the engineered strategies that improve viral potency and safety, explore current clinical progress, and assess the potential of combination treatments. OVs mainly work through a two-pronged approach by direct killing or immunogenic cytolysis. By releasing tumor-specific antigens and pro-inflammatory signals, OVs change the cold tumor microenvironment into a hot one, drawing T-cells to attack both the main tumors and distant metastases. This review also explores key viral platforms, including the common virus like the Adenovirus, Vaccinia virus, Herpes Simplex Virus (HSV-1) and Reovirus, across various cancers such as melanoma, glioblastoma and solid tumors. Clinical translation has advanced from an anecdotal reports to over 250 active trials worldwide. While Imlygic remains a landmark FDA-approved treatment for melanoma, newer platforms like Delytact and H101 have received regional approvals. Key findings show that OVs are more effective when they are in synergy with immune checkpoint inhibitors like Pembrolizumab, that helps in achieving objective response rates (ORR) of up to 62% in advanced melanoma. However, challenges persist, including neutralization by host antibodies, physical barriers like high interstitial fluid pressure and scalability issues in manufacturing. Oncolytic virotherapy is now progressing to its next iteration, evolving from simple cytolytic agents to advanced programmable, biological platforms. Emerging trends, such as personalized neoantigen encoding and real-time monitoring with reporter genes, may help overcome the existing delivery challenges. Integrating OVs with precision medicine and multimodal therapies is shaping the strategy for achieving durable clinical responses in the changing field of oncology.

Keywords

Oncolytic virus; Herpes simplex virus; Virotherapy; Melanoma; T-VEC

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Introduction

In 2023 studies have shown that, global cancer cases have reached approximately 18.5 million new diagnoses annually, with deaths exceeding 10 million per year and many conducted studies showing projections that by 2050, new cases could surge well over 30 million with 40% rise in fatalities [1], [2]. There are rising incidence of 'early-onset cancers' - cancers diagnosed in adults under age of 50, particularly gastrointestinal and breast cancers creating a 'sandwich generation' of patients juggling with career, child-raising, and aggressive treatment [1]. While an estimated 40% of cancer deaths are linked to modifiable risk factors – such as the use of tobacco products, hyperglycaemia, and obesity which highlights a gap in public health prevention [1], [4]. Surgery, chemotherapy, and radiation are often designated as the 'three pillars' of conventional oncology treatment but despite their life-saving potential, they have foundational biological and clinical limitations [2], where one primary issue is the lack of specificity i.e. 'the shotgun' approach, known for causing collateral damage to the patient as these treatments cannot distinguish between a cancer cell and a healthy fast-growing cell leading to severe side effects like systemic toxicity - like alopecia, anemia, immunosuppression, and organ damage with procedures like the likes of chemotherapy and radiotherapy and surgeries being ineffective against micro metastasis [6], [7], [8]; and other concern involved is of the 'cancer Stem Cells' (CSCs), where the conventional therapies excel at shrinking the bulk of a tumor, but often fail to kill CSCs that are frequently resistant to chemo and radiation and even if few of these cells survive, they stay latent for years before reawakening leading to relapse that is often more aggressive and drug-resistant than the original tumor [9], [10], [11], [12]; another resistance mechanisms is that tumors are not uniform they are heterogeneous, though the treatment may kill 99% of sensitive cancer cells, but the remaining 1% of resistant cells survive and multiply [13], [14], [15], [16]; while modern medicine is moving toward immunotherapy, conventional treatments can sometimes hinder it, whereas many case analysis have shown that high-dose chemotherapy destroys the very immune cells i.e. T-cells needed for the body to fight the cancer naturally [3], and also another limitation is the chronic Inflammation i.e. radiation can cause localized fibrosis and inflammation, which may inadvertently create a "shield" around the tumor, making it harder for immune cells or newer drugs to penetrate and kill it [4]; Sometimes physical and biological barriers also restrict the conventional approach for example the Tumor microenvironment often have high internal pressure and poor blood vessel structure, which prevents drugs from reaching the centre of the mass [19], [20].

Oncolytic viruses are specialized agents that selectively infect and kill cancer cells. Once inside, the virus replicates and causes the cell to burst, discharging new viral particles that can infect other cancer cells. This process, known as oncolysis, not only kills the tumor cells but also stimulates the host immune system to detect and neutralize the tumor potentially enhancing anti-tumor immunity [21], [22], [23]. While the concept of using oncolytic virotherapy dates back over a century, the field methods has evolved from using 'accidental' viral infections to sophisticated, genetically 'armed' immunotherapies [24]; many examples of virotherapy against cancer has been dated as early as the 1900s even before conventional treatment [25].

The evolution of oncolytic virotherapy is typically divided into four distinct eras –

i) Anecdotal observations (Late 1800s – 1940s) where the field began with spontaneous remissions as physicians observed and analyzed that some cancer patients did experienced temporary tumor shrinkage after contracting viral infections like influenza or measles like for example a case in 1912 where Italian physicians reported that the rabies vaccine caused regression in cervical cancer patients [7].

ii) Wild-type virus trials (1950s – 1980s) where human trials began with viruses like West Nile, Hepatitis with some mixed results as the immune system would clear out the viruses before it could have any impact; and by the 70s the interests waned as chemotherapy became the standard of care [26], [27].

iii) Genetic engineering (1990s – 2010s) where in 1991 the first genetically modified OV, a Herpes simplex virus lacking the thymidine kinase gene as shown to have selectively kill brain tumor cells in mice [7] and in 2015 the first oncolytic virus approved for clinical use was *Talimogene laherparepvec* (T-VEC), a modified form of HSV-1 designed for treating melanoma that has demonstrated effectiveness in reducing tumor size and improving overall survival in patients with advanced melanoma [28], [29], though in 2004/05 Rigvir in Latvia [8] and H101 from China [[9], [30]] became the first one of those OVs to be granted for therapeutic application though it was not widely recognised.

iv) Armed immunotherapy (2020-Present) where in today's era OVs are no longer just 'cell killers' but as 'immunotherapy primers' [[5], [31]] also called Trojan Horses by scientists to deliver Cytokines like GM-CSF to elicit an immune response [[10], [32]] and also OVs alongside drugs like Pembrolizumab are used to turn cold tumors (invisible to the immune system) into hot tumors [[11], [33]]. So, oncolytic virus therapy currently represents a transformative shift in oncology, often referred to as the new frontier of cancer therapy following chemotherapy and targeted therapy [[12], [13], [34], [35]].

The rationale for using these viruses in malignant tumors is built on a dual mechanism of action: direct physical destruction of the tumor and subsequent 'awakening' of the host's immune system [36], [37], [38]. The primary rationale lies in the inherent or engineered ability of certain viruses to distinguish between healthy and malignant cells - a concept known as 'Selective Oncotropism' and key supporting factors include –

i) Defective Antiviral Pathways as to prioritize rapid growth most malignant tumors lose its natural defence mechanisms like the abrogation of Type I Interferon pathway. This makes them a 'soft target' where the viruses can replicate unchecked, whereas healthy cells can still block viral entry or replication [39], [40].

ii) Metabolic Vulnerabilities is another reason where the viruses can be engineered to depend on tumor-specific enzymatic signatures for viral replication e.g. the thymidine kinase or to exploit pathways like RAS/RAF/MEK, which are hyperactive in many cancers and lastly [41].

iii) Surface Receptors as many OVs are designed to bind specifically to receptors that are highly concentrated on tumor surfaces e.g. the CD155 in glioblastoma [42].

Another ground for selection of OVs in malignant cancer therapy is non-overlapping toxicity. Unlike chemotherapy, OVs generally do not cause systemic immunosuppression; they can be used alongside traditional treatments to enhance their efficacy without doubling the side-effect profile [43]. Furthermore, modern OVs act as 'trojan horses.' That is, they can be potentially to carry 'payloads' such as genes that produce GM-CSF (to recruit immune cells) or proteins that block TGF-beta (which tumors use to hide from the immune system) [[17], [44]].

The primary goal of the review is to evaluate the therapeutic potential and effectiveness of oncolytic viruses (OV's) as an emerging modality in cancer therapy. Specifically, the review aims to - Evaluate the efficiency to assess the current efficacy of various oncolytic viruses in treating malignant tumors also analysing in detail the biological mechanisms that allow OVs to singularly target the cancer cells while sparing the healthy host tissues and to evaluate the recombinant methodologies to review how genetic modifications are utilized to enhance the safety, selectivity, and potency of viral platforms. Then finally investigation of the clinical progress done to present an outlined summary of completed and ongoing clinical trials, along with the current regulatory status of approved therapies like 'Imlygic' and simultaneously assessing combination therapies that explore the synergistic effects of combining OVs with traditional treatments such as chemotherapy, radiotherapy, and modern immunotherapies like checkpoint inhibitors.

The scope encompasses a comprehensive analysis of the field, ranging from fundamental biology to clinical application. Key areas include the review and study of the platforms of various virus types used in therapy, including Adenoviruses, Herpes Simplex Virus (HSV), Reovirus, and Vaccinia virus and the review of different tumor types which includes the evaluation of OV efficiency across diverse malignancies, specifically solid tumors (e.g., glioblastoma, melanoma, breast, lung, and colorectal cancers) as well as haematological and paediatric cancers. Also, analysis of administration routes (intra-tumoral vs. systemic) and the physical or biological barriers that affect viral delivery to the tumor site. Discussion of biosafety concerns, potential off-target effects, host immune responses, and the ethical challenges of using engineered viruses. While ending the review with future trends which includes the identification of emerging trends such as personalized oncolytic virotherapy and the advancements in precision oncology.

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Biology of oncolytic viruses

An oncolytic virus is a virus that preferentially infects and lyses (breaks down) cancer cells. The oncolytic effect occurs through two primary phases – 'direct oncolysis' where the virus enters the cancer cell, hijacks its machinery to replicate, and eventually causes the cell to lyse, releasing new viral particles to infect neighbouring tumor cells [44], [45]. Another one is the cell death wherein as the cancer cell dies, it releases tumor-specific antigens and danger signals which activates …

Types of oncolytic viruses used in cancer therapy

The clinical efficiency of OVs is demonstrated by their potential ability to trigger objective response rates (ORR), often in combination with other immunotherapies like checkpoint inhibitors [90], [91].

The table (Table 6) summarizes some of the most prominent OVs currently in development or approved for clinical use, detailing their source virus type and target cancer.

The table below (Table 7) summarizes some of the most prominent OVs currently in development or approved for clinical use …

Genetic engineering interventions to enhance efficiency

Genetic engineering has transformed oncolytic viruses (OVs) from simple pathogens into sophisticated 'precision-guided' cancer therapeutics [12]. While naturally occurring viruses can infect cancer cells as they most of the time don't have the specificity or potency required for clinical success, strategies to enhance efficiency focus on four pillars that are selectivity which ensures they only replicate in cancer, potency that increases viral spread in the tumor, safety is the strategy which …

Delivery strategies and bio-distribution

Oncolytic virotherapy represents a transformative rim in accurate oncology, utilizing both natural and engineered viruses for selectively infection, replication and destroy the malignant tumors [12]. Beyond direct oncolysis, some of these agents act as potent 'in situ vaccines' releasing TAAs and danger signals that transform the TME into an immunologically 'hot' landscape [41]. However, the journey of an oncolytic viruses from the point of administration to the tumor site is accompanied by …

Clinical trials and regulatory status

Oncolytic viruses represent a breakthrough in cancer immunotherapy, utilizing genetically modified or naturally occurring viruses to selectively infect and simultaneous lysis of cancer cells while sparing healthy tissue. As of 2026, the regulatory status of OVs remains concentrated around a few landmark approvals – the Talimogene laherparepvec remains the primary therapy approved by both the FDA and EMA for unresectable melanoma [179] while regional approvals include the H101 (Oncorine) in …

Combination therapy

Oncolytic viruses (OVs) offer a versatile platform in precision oncology, especially in multimodal regimens [195]. OVs selectively infect and lyse cancer cells, augmentative effects have been observed when combined with other therapies [196]. Paired with chemotherapy or radiotherapy, OVs act as radiosensitizers or chemosensitizers by inhibiting DNA repair, intensifying tumor vulnerability to the cytotoxic damage [197], [198]. While integration with immunotherapy like immune checkpoint …

Safety, toxicity and ethical consideration

Oncolytic viruses (OVs) represent a frontier in precision medicine; using native or genetically modified viruses to selectively and concurrently infect and lyse tumors while sparing healthy tissue; however, their clinical integration is managed through a rigorous framework of safety, toxicity, and ethical oversight [34], [204], [205]. One of the main issues is the biosafety and off-target effects where the primary safety concern involves off-target infection as while major OVs are designed for …

Limitation and future outlook

Oncolytic viruses hold immense promise as targeted cancer therapies by selectively infecting and lysing tumor cells, yet noteworthy complications have been encountered that disrupted the clinical trials and usage. A primary challenge is the tumor heterogeneity and resistance, as cancers exhibit diverse genetic and phenotypic profiles within and across patients. This variability allows some tumor subpopulations to evade the oncolytic virus infection through mutations in viral entry receptors of …

Conclusion

Oncolytic virotherapy has evolved from clinical observations into a detailed and programmable part of modern cancer treatment. By using both direct tumor destruction and inducing immunogenic cell death, these viruses can instigate the immune system against hidden tumors that were invisible to the immune system, creating a quick and potentially long-lasting immune responses against tumors. The success of treatments like Imlygic, Delytact, and H101 highlights the potential of using Herpes Simplex …

CRediT authorship contribution statement

Subham Das: Writing – original draft, Data curation. **Himakshi Rekha Goswami:** Writing – review & editing, Writing – original draft. **Indrani Barman:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **Nayan Talukdar:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. …

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