

Covid Research and Treatment

Research Article

Oncolytic Virus Therapy: A Review

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Abstract

Oncolytic viruses (OVs) have emerged as promising therapeutic agents for the treatment of malignant tumors due to their ability to selectively infect and lyse cancer cells while sparing normal tissues. In addition to their direct oncolytic activity, OVs stimulate both innate and adaptive antitumor immune responses, making them an attractive platform for targeted cancer therapy. The therapeutic efficacy of OVs depends primarily on their tumor selectivity and their capacity to enhance tumor cell destruction through multiple mechanisms. Advances in molecular biotechnology and genetic engineering have enabled the modification of wild-type viral strains to improve tumor specificity, increase therapeutic potency, reduce toxicity, and enhance safety profiles, thereby facilitating their evaluation in clinical trials. This review provides a comprehensive overview of oncolytic virotherapy, including its mechanisms of action, clinical applications, combination treatment strategies, current challenges, and future prospects. Moreover, combining OVs with conventional therapies such as chemotherapy, radiotherapy, immune checkpoint inhibitors, and targeted therapies has shown synergistic antitumor effects and enhanced therapeutic efficacy. Certain oncolytic viruses are also capable of inducing durable antitumor immune memory, thereby reducing the risk of tumor recurrence and metastasis. Despite these advances, the clinical translation of oncolytic virotherapy in veterinary medicine remains limited. Although promising results have been obtained in preclinical studies, further research is required to establish its safety, efficacy, and practical application in veterinary oncology. One of the major obstacles to successful virotherapy is the efficient and targeted delivery of viruses to tumor sites. Systemic administration is often hindered by pre-existing antiviral immunity, rapid viral clearance, and limited tumor penetration, whereas intratumoral administration is invasive, technically challenging, and costly. Consequently, the development of effective viral delivery systems capable of overcoming these barriers remains a critical research priority. Continued advances in viral engineering, immunotherapy, and targeted delivery technologies are expected to accelerate the clinical translation of oncolytic virotherapy, making it an increasingly important component of future cancer treatment strategies in both human and veterinary medicine.

Keywords: Oncolytic viruses, Oncolytic virotherapy, Cancer therapy, Immunotherapy, Clinical applications, Veterinary oncology.

Introduction

Until the early twentieth century, surgical resection was the primary treatment modality for cancer. Subsequently, advances in oncology led to the development of radiotherapy, chemotherapy, targeted therapy, immunotherapy, and other multimodal treatment approaches, substantially improving cancer management. Nevertheless, the limitations of con-

ventional therapies including nonspecific toxicity, therapeutic resistance, tumor recurrence, and metastasis have driven the search for more selective and effective treatment strategies. Oncolytic virotherapy has emerged as one such promising approach, utilizing naturally occurring or genetically engineered viruses that selectively infect and destroy malignant cells while simultaneously stimulating robust antitumor

immune responses. Although the concept of using viruses to treat cancer dates back to the late nineteenth century, recent advances in molecular virology, genetic engineering, and cancer immunology have significantly accelerated the clinical development of oncolytic viruses, leading to several successful clinical trials and regulatory approvals for selected malignancies [1,2,3].

The concept of using viruses as anticancer agents has been explored for more than a century. Early clinical observations documented that some patients with leukemia and lymphoma experienced transient tumor regression following naturally acquired viral infections, suggesting that viruses possessed the ability to selectively target malignant cells. These observations provided the foundation for the subsequent development of oncolytic virotherapy [4,5]. These findings prompted early clinical attempts to deliberately infect cancer patients with wild-type viruses. Although temporary antitumor responses were occasionally observed, these approaches were associated with significant toxicity, including severe viral illness and, in some cases, treatment-related mortality, owing to the lack of tumor specificity and inadequate understanding of viral biology. Subsequent studies involving patients with solid tumors, including cervical cancer, demonstrated the ability of certain viruses to infect and destroy tumor cells; however, these early therapies failed to produce durable clinical responses or improve overall survival. Advances in molecular virology, genetic engineering, and cancer immunology have since enabled the development of genetically modified oncolytic viruses with enhanced tumor selectivity, improved safety, and greater therapeutic efficacy, transforming oncolytic virotherapy into a promising modality for modern cancer treatment [5,1].

The first successes in virus cancer therapy were achieved in the 1970s using the mumps virus. Because mumps itself causes serious disease, use of an unaltered version of this virus was not a good idea. Since that time, many animal and human viruses have been investigated for their ability to kill cancer cells [4,6].

The path toward the clinical approval of oncolytic viruses (OVs) has been long and challenging. The first regulatory approval of an oncolytic virus was granted in China for the recombinant adenovirus H101, marking a significant milestone in the development of virotherapy [1]. Since then, oncolytic virotherapy has emerged as a promising therapeutic strategy for cancer treatment, with the potential to become an important component of precision oncology. The development of OVs has not only expanded the therapeutic landscape of cancer management but has also introduced a novel paradigm that combines direct tumor lysis with the activation of systemic antitumor immunity. Consequently, oncolytic virotherapy is increasingly recognized as a major advancement in cancer treatment alongside conventional chemotherapy, targeted therapy, and immunotherapy. Currently, several viral platforms including herpes simplex virus, adenovirus,

vaccinia virus, reovirus, picornavirus, and poxvirus are under investigation in preclinical studies and human clinical trials, with several candidates progressing through late-stage clinical development [2,3]. Although clinicians first reported spontaneous tumor regression following natural viral infections more than a century ago, only recent advances in molecular virology, genetic engineering, and tumor immunology have enabled the successful clinical translation of oncolytic viruses. Notably, the granulocyte-macrophage colony-stimulating factor (GM-CSF)-expressing herpes simplex virus talimogene laherparepvec (T-VEC) became the first oncolytic virus approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced melanoma, demonstrating the clinical potential of genetically engineered OVs [1,2]. This review summarizes the latest advances in the clinical applications and ongoing clinical trials of oncolytic viruses while highlighting current challenges and future perspectives for their successful translation into routine cancer therapy.

Mechanisms of Oncolytic Viro Therapy

Oncolytic virus (OV) therapy is based on the selective replication of viruses within cancer cells and their subsequent intratumoral spread, while sparing normal healthy tissues [5,7]. These viruses are naturally occurring or can be modified to selectively infect and destroy cancer cells. In addition, there's evidence that OVs can stimulate the host's immune response to combat tumors [8]. The anticancer mechanisms of the OVs include direct oncolysis or cytotoxicity toward the cancer cells or indirect induction of bystander effects (including the destruction of tumor blood vessels) [9]. The principle of this therapy is that oncolytic virus that has been attenuated inside the laboratory is centered for specific seek targets to infect most cancer cells and it begin to replicate in most cancer cells and then release the signal, activate the immune mechanism within the body, and subsequently perform oncolysis to kill cancer cells. Studies have shown that oncolytic viruses can kill cancer through the two primary mechanisms of direct cell lysis and the induction of antitumor immune responses [10].

Tumor cell lysis

Virus replication in infected tumor cells results in apoptosis and cell lysis (Figure 1). Following viral replication within tumor cells and subsequent lysis, newly produced viral particles propagate the lytic cycle by infecting adjacent cancer cells, thereby amplifying the therapeutic effect within the tumor microenvironment [5,7,3]. The viral lytic cycle continues until inflamed host cells are depleted, or antiviral immune responses attenuate virus replication [11]. Immune responses can also result in the dying of tumor cells by way of breaking the tolerance of tumor cells [12]. Non-infectious host cells can also be affected by oncolytic viruses in need of treatment. In this context, it has been disclosed that the onco-

lytic vaccine virus can interrupt tumor angiogenesis, reduce blood flow to most cancer cells, and in long run purpose hypoxia by affecting vascular cells, all of which are associated with inhibiting tumor growth and progression (Breitbart et al., 2007). Although lysis of tumor cells through the initiation of the lytic cycle is one of the inherent characteristics of oncolytic viruses, evidence suggests that in addition manipulations can increase their lytic capacity (Goradel et al., 2018).

Enhancement of anti-tumor immune responses

The second mechanism of action oncolytic viruses is to enhance antitumor immune responses (figure 1). Studies have shown that following infection of tumor cells with oncolytic viruses, cell death and the liberate of tumor-related antigens along with viral pathogen-associated molecular patterns (PAMPs) and different cellular danger-associated molecular patterns (DAMPs) lead to the enhancement of tumor specific immune responses and the killing of remote and noninfectious tumor cells (Pol et al., 2012). Tumor cell lysis can also induce the production and secretion of inflammatory mediators, including type I interferons, interferon-gamma (IFN- γ), interleukin-12 (IL-12) and tumor necrosis factor- α (TNF- α) [13,3].

The philosophy of the use of engineered oncolytic viruses is to beautify immune responses similarly. In this strategy, the insertion of an immune-stimulating molecule into the oncological genome of viruses could change the immune-sup-

pressive tumor microenvironment in favor of treatment. As formerly referred to, GM-CSF is the most obvious example of this type of genetic engineering. After incorporating the GM-CSF gene into the oncolytic genome, viruses can act as an immune responses stimulator, leading to the maturation and recruitment of antigenpresenting cells (APCs), particularly DCs, inducing antitumor effector T cells and NK cells which are specific for tumor antigens (Jhawar et al., 2017). In order to enhance and increase the delivery of intracellular antigen to the proteasome and antigen presentation, the oncolytic adenovirus genome was modified for competitive inhibition of deoxyguanosine by means of conversion to monophosphates, which can also disrupt and terminate DNA synthesis by interfering with proliferating cell DNA, resulting in cell death [5,14]. Another well-studied suicide gene is cytosine deaminase (CD), which converts the non-toxic prodrug 5-fluorocytosine into the highly cytotoxic 5-fluorouracil with strong antitumor activity (Freytag et al., 2002,5]. The insertion of the adenovirus death protein (ADP) gene into the adenoviral genome enhances viral replication and increases the lytic activity of the virus, thereby improving tumor cell killing efficiency [15]. Oncolytic viruses selectively infect and replicate within tumor cells, leading to cancer cell lysis and release of tumor-associated antigens, cytokines, chemokines, and damage-associated molecular patterns (DAMPs), which stimulate systemic antitumor immune responses and may contribute to elimination of distant metastases (Figure 1).

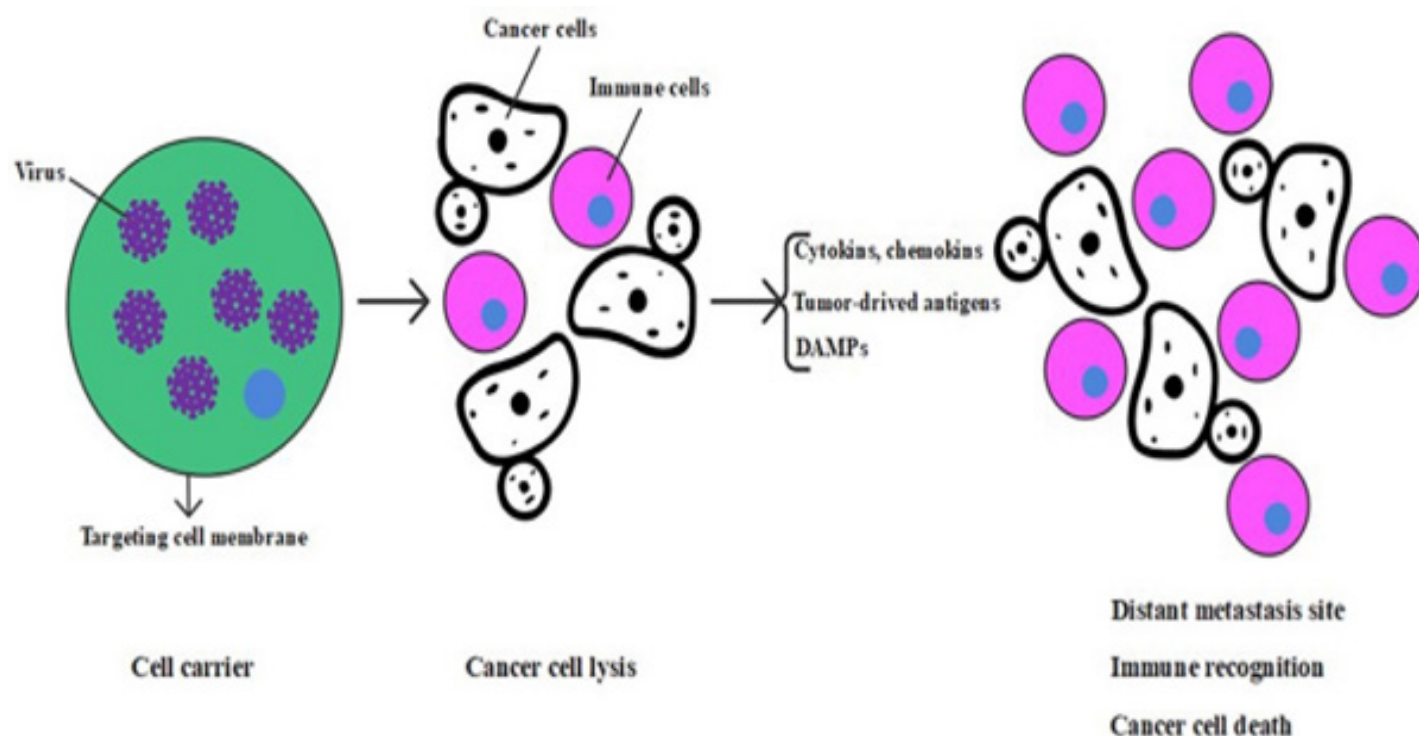


Figure1: Anticancer mechanisms of oncolytic viruses (OVs)

Sources (Freytag et al., 2002,5,Guo et al., 2022)

Applications Of Oncolytic Viruses: An Overview Of Current Clinical Trials

One of OV's applications in precise tumor imaging was fluorescence imaging (L. Quillien et al., 2021). The green fluorescent protein, which is derived from marine invertebrate organisms, may be used to reveal tumor behaviors. Oncolytic viruses, primarily based on developing frame of preclinical and medical proof, might be a particularly successful new cancer therapy (Zheng et al., 2019). Nowadays, herpes viruses, adenoviruses, coxsackie viruses, poxviruses, polioviruses, measles viruses, reoviruses, and Newcastle disease viruses are some of the OVs under observe for most cancer therapy [13].

Oncolytic viruses (OVs) exert their anticancer effects through multiple complementary mechanisms. The primary mechanism is direct oncolysis of tumor cells following selective viral replication, which leads to various forms of programmed and non-programmed cell death, including apoptosis, necrosis, pyroptosis, and autophagic cell death. Notably, the dominant mode of cell death may vary depending on the specific oncolytic virus and tumor microenvironment. In addition to direct cytolysis, OVs can disrupt tumor-associated vasculature and inhibit angiogenesis, thereby compromising tumor blood supply and inducing secondary apoptotic and necrotic death in both infected and neighboring uninfected cells. Furthermore, OVs promote robust antitumor immunity by activating innate immune responses and enhancing tumor-specific adaptive immune effector functions, resulting in immune-mediated cytotoxicity against both malignant and stromal components of the tumor microenvironment [16,17,18].

Cancer has always been an enormous threat to human health and survival. In recent years, accurate tumor imaging using OV has attracted more and more attention. OVs with precise genes can selectively infect tumor cells and replicate within them or express genes of interest such as luciferase reporter gene and human Na⁺/I⁻ symporter (hNIS) gene. The emergence of oncolytic viruses provided a new strategy for us to alleviate or even cure malignant tumors. An oncolytic virus can be described as a genetically engineered or naturally existing virus that can selectively replicate in cancer cells and then kill them without damaging the healthy cells [9].

Pancreatic cancer

Worldwide, the occurrence of pancreatic cancer is low, and the disease is not recommended for screening by the World Health Organization (Capurso et al., 2015). The survival rate of pancreatic ductal adenocarcinoma, responsible for 95% of pancreatic cancers is 6% in 5 year and the only potential cure for pancreatic ductal adeno - carcinoma (duodeno-pancreatectomy) does not offer a big change in mortality (Becker et al., 2014). Pancreatic cancer has been known as a malignant form of cancer with a poor prognosis and treatments

that in the majority of patients ends with death. Pancreatic cancer is very resistant to treatment and its survival rate is one of the lowest among all cancers [19]. One idea is to use viruses as oncolytic agents to create the least side effects in the patient along with recovery from this disease [20].

Breast cancer

Breast cancer is a heterogeneous disease where the majority of tumors are immunologically "cold," and therefore using immune therapeutics within breast cancer appeals to be much less compelling than those of melanoma or lung cancer. However, OV has a capacity to make "cold" tumors "hot" by reprogramming the TME in patients whose tumors are cold. OV has been shown to modulate the tumor microenvironment (TME), causing an increase in pro-inflammatory cells (e.g., cytotoxic T cells, macrophages) that could potentially turn a "cold" tumor into a "hot" one (Samson et al., 2018). In breast cancer, there are some preclinical studies using oncolytic virotherapy as well as a few early-phase clinical studies with promising early markers of response (Zamarin et al., 2014).

Melanoma

Metastatic melanoma continues to be one of the most difficult to treat cancers because it is often insensitive to chemotherapy, can be highly aggressive, and can require several different types of treatment depending on the stage and location of the disease and health status of the patient. Despite new therapeutic options, additional treatments are needed, particularly for patients with metastatic disease [21]. In 2015, the first oncolytic viro therapeutic agent, talimogene laherparepvec (T-vec), was approved by the FDA for use in metastatic melanoma. T-vec is a modified oncolytic HSV that expresses the granulocyte-macrophage colony-stimulating factor (GM-CSF). This virus contains mutations in infectious cell proteins 34.5 and 47, which allow the virus to selectively infect tumor cells and inhibit tumor cell expression of major histocompatibility complex class I antigens. This serves to initiate a specific immune response against only tumor cells infected by the virus [22].

Combination therapy

Radiotherapy combined with oncolytic virotherapy exhibits synergistic antitumor activity in multiple tumor models due to enhanced viral spread, immunogenic cell death, and increased tumor sensitivity to radiation [16,17]. In one case, the synergistic impact between radiotherapy and virotherapy was observed with oncolytic HSV (Adusumilli et al., 2017). Radiotherapy enhances oncolytic virotherapy through multiple complementary molecular and cellular mechanisms. Recent studies suggest that radiation-induced stress responses can upregulate viral gene expression and promote tumor

susceptibility, including modulation of host DNA damage response pathways such as GADD34 signaling and activation of stress-related kinases (e.g., p38 MAPK), which enhance viral promoter activity and replication efficiency within tumor cells. In addition, oncolytic herpes simplex virus (oHSV) has been shown to interfere with DNA repair mechanisms, thereby increasing radiation-induced cytotoxicity and tumor cell vulnerability. These effects collectively contribute to improved viral spread and enhanced tumor control. Furthermore, radiotherapy has demonstrated synergistic interactions with oncolytic vaccinia virus, leading to increased therapeutic efficacy. Across preclinical and translational studies, combined oncolytic virotherapy and radiotherapy consistently results in significant tumor growth delay and improved survival compared with monotherapy, supporting its potential as a promising combinational cancer treatment strategy [18,17,23,24]. These findings suggest that virus-mediated downregulation of anti-apoptotic proteins may enhance the sensitivity of tumor cells to the cytotoxic effects of ionizing radiation, thereby increasing radiation-induced cell death and therapeutic efficacy. Preclinical and translational evidence further indicates that combining oncolytic virotherapy with radiotherapy produces additive or synergistic antitumor effects in both in vitro and in vivo models, mediated through enhanced immunogenic cell death, modulation of tumor survival signaling, and improved tumor microenvironment reprogramming [24-27].

Oncolytic Virotherapy in Veterinary Medicine

The traditional methods used for the treatment of cancer in companion animals mainly include surgery, chemotherapy, radiation therapy, and hyperthermia. However, advanced-stage cancers in dogs and cats are often associated with a poor prognosis. Many naturally occurring cancers in companion animals closely resemble their human counterparts with respect to histopathological characteristics, biological behavior, genetic alterations, risk factors, molecular pathogenesis, and therapeutic response, making them valuable translational models for comparative oncology (Paoloni & Khanna, 2008; 28). Although numerous clinical trials of oncolytic viruses have been conducted in humans, clinical studies in companion animals remain limited. For example, intravenous and intratumoral administration of the Lasota strain of Newcastle disease virus in dogs with cutaneous lymphoma resulted in regression of existing lesions and no development of new lesions during a four-week follow-up [29]. Recent reviews emphasize that veterinary clinical evaluation of oncolytic virotherapy is still in its early stages despite its considerable potential for treating naturally occurring cancers in dogs and cats [1,30].

Oncolytic Viro therapy in Canine Cancer

Adenoviruses are also being investigated as therapeutic agents for canine cancers. Human adenovirus serotype 5

(HAdV-5) has been shown to productively replicate in canine osteosarcoma and canine mammary carcinoma cells [31]. Recent studies in comparative and veterinary oncology continue to demonstrate the feasibility of adenovirus-based platforms for treating spontaneous tumors in dogs, highlighting their translational relevance and tumor-selective replication potential (Hoffman et al., 2022; Cekanova et al., 2023; 30). Furthermore, canine adenovirus type 2 (CAV-2), transcriptionally targeted to canine osteosarcoma cells through the insertion of the osteocalcin promoter, has been evaluated as a potential therapeutic agent for canine osteosarcoma. Recent studies have highlighted the growing potential of adenovirus-based oncolytic virotherapy in veterinary oncology, particularly for the treatment of canine solid tumors, although clinical translation remains in its early stages [30,1].

Challenges Associated with Oncolytic Viro Therapy and Post Delivery Strategies

The major challenge in this therapy is the targeted delivery of the virus into the tumor. In most cases, systemic administration does not work well due to preexisting immunity. Therefore, virus delivery needs to be improved for effective systemic administration since intratumoral administration is expensive and difficult especially in cases of malignant gliomas. Some of the novel approaches involve the use of nano particles, complex viral particle ligands, and immuno-modulatory agents. Delivery of the virus into the tumor via nano particles uses a technologically complex image-guided delivery system. Alternatively, to secure the delivery of the oncolytic viruses via the blood stream, carrier cells that possess inherent tumor tropism have also been considered (Roy et al., 2013). Another challenge is the optimization of combination therapies using oncolytic viruses along with the chemotherapeutic or immunotherapeutic drugs to get better and stable results. Immune response induction by oncolytic viruses after infection suppresses the replication of the virus thereby posing a hindrance to the effective functioning of the biotherapy intended to treat cancer [32].

Oncolytic viruses (OVs) are not a “magic bullet” for cancer therapy, as the antitumor activity of most OV monotherapies remains modest. One of the major challenges in oncolytic virotherapy is achieving efficient and accurate delivery of the virus to tumor sites. Systemic administration, particularly via the intravenous (IV) route, is considered the most clinically desirable approach; however, intravenously administered OVs must overcome several biological barriers, including sequestration by the liver and clearance by the mononuclear phagocyte system, before reaching tumor tissue. Additional limitations affecting therapeutic efficacy include viral tropism, delivery platforms, biodistribution, dosing strategies, antiviral immune responses, and the optimization of virus-mediated oncolysis [1,30].

In solid tumors, there is a range of hurdles that the OV need

to stay away from to attain the tumor site. First, physical barriers post a big challenge to delivery because viruses must get past the endothelial layer to reach the target cells [33]. In addition, the abnormal lymphatic networks and vascular hyper permeability inside tumors and the dense extracellular matrix (ECM) of solid tumors leading to interstitial hypertension [8] which can impair viral infiltration. Furthermore, OV's can result in a strong innate immune response due to interactions among them and antigen-presenting cells (APCs), together with enormous antiviral immunity, preexisting circulating antibodies, and blood factors such as the coagulation factors FIX, FX, and complement protein C4BP. Subsequently, OV's are more likely to be cleared by the host's immune system, and it is difficult to make sure whether sufficient numbers reach the tumor site [34].

Hypoxic Effects

Hypoxia is a hallmark of solid tumors that develops during tumor progression and has complex and sometimes contradictory effects on the efficacy of oncolytic viruses (OV's). In many cases, hypoxic conditions impair the replication and lytic activity of adenoviruses without significantly altering the expression of viral entry receptors. Moreover, because hypoxia can induce cell-cycle arrest and extensive metabolic reprogramming, it may reduce the replication efficiency of adenoviruses and other oncolytic viruses that depend on actively proliferating host cells for productive infection [1,30,16].

Immune Responses

Another challenge in the use of OV's is preexisting immunity because of previous immunization or infection leading to short half-life following intravenous delivery. Coating oncolytic adenoviruses with polymers are referred to as "stealth-ing", can protect adenoviruses during delivery [35]. The most commonly utilized polymers include N-(2-hydroxypropyl) methacrylamide (HPMA), polyethylene glycol (PEG), and polyamidoamine (PAMAM). In addition to prolonging viral cir-

culatation time, polymer modification of oncolytic adenoviruses can enhance tumor targeting and improve delivery efficiency through altered biodistribution and reduced immune recognition [30].

Choosing Patients

Assuming that all other challenges are addressed, a critical question remains: which patients are most suitable for oncolytic virotherapy? To date, no validated predictive biomarkers have been established to reliably identify patients who are likely to respond to oncolytic virus (OV) treatment. Furthermore, because most OV's remain under clinical investigation, patients receiving oncolytic virotherapy have often undergone multiple lines of conventional treatments, including chemotherapy, radiotherapy, targeted therapy, or immunotherapy. These prior treatments can profoundly alter both the tumor microenvironment and the patient's immune system, potentially influencing the therapeutic efficacy of OV's [36].

Spread and Penetration

In carcinomas, intercellular junctions between epithelial cells, particularly tight junctions, constitute a significant barrier to the penetration of high-molecular-weight therapeutic agents, thereby limiting drug delivery and contributing to therapeutic resistance [37,38]. Furthermore, phenotype shifts for duration of metastasis through epithelial-to-mesenchymal transition and then mesenchymal to epithelial transition tighten epithelial junctions and makes treatment complicated. Epithelial junctions also act as a barrier to intracellular penetration of OV's, especially adenoviruses [39]. Some types of adenovirus including HAdV-B3, B14, and B14p may overcome the junctions by liberating penton-dodecahedra (Pt-Dd) in the early phase of infection and before cell lysis, while non-Pt-Dd generating adenoviruses generate an excess of the fiber protein at the same stage. Table 1 show challenges associated intravenous and intratumoral administration of OV's and their possible strategies.

Intravenous		Intratumoral	
Challenges	Strategy	Challenges	Strategy
Immune surveillance (constant circulation of immune cells)	Viral shielding	Tumor microenvironment structure (immunosuppressive environment)	Exercise
Viral antibodies (rapid neutralization)		Extracellular matrix (ECM) (reduced viral propagation)	Drugs to alter ECM and TME architectural
Lack of guided delivery system (small payload to target site)	Magnetic guided delivery system	Inaccessible tumors (poor and painful drug delivery)	
Tumor penetration (collapsed vasculature)	Increased penetration via ultrasound	Invasive (spread beyond primary tissue)	Alternative routes of administration

Source [40]

Table1: Challenges and strategies in overcoming restricted delivery of oncolytic viruse

Conclusion And Future Perspective

Oncolytic virotherapy has emerged as a promising and innovative approach to cancer treatment, offering selective tumor cell destruction while simultaneously stimulating antitumor immune responses. The clinical success of several oncolytic virus (OV) based therapies, including regulatory approval of selected agents, has demonstrated the feasibility and therapeutic potential of this strategy. Compared with conventional treatment modalities, oncolytic viruses provide a unique mechanism of action that combines direct oncolysis with immune activation, making them attractive candidates for the treatment of a broad range of malignancies. Despite these advances, several challenges remain before oncolytic virotherapy can be widely adopted as a standard treatment. Current research is focused on improving viral delivery, enhancing tumor specificity, overcoming antiviral immune responses, and increasing therapeutic efficacy. One promising strategy involves combining OVs with immune checkpoint inhibitors, chemotherapy, radiotherapy, targeted therapies, or genetically engineered therapeutic transgenes to achieve synergistic antitumor effects. Although the results of preclinical studies and clinical trials have been encouraging, additional large-scale clinical investigations are required to establish the long-term safety, efficacy, and optimal therapeutic regimens of different OV platforms across diverse cancer types. Continued advances in virology, immunology, synthetic biology, and precision medicine are expected to facilitate the development of next-generation oncolytic viruses with enhanced therapeutic properties. In conclusion, oncolytic virotherapy represents a rapidly evolving field with considerable potential to transform cancer management. As our understanding of tumor biology and virus-host interactions continues to expand, and as ongoing clinical trials provide further evidence of safety and efficacy, oncolytic viruses are expected to become an integral component of multimodal cancer therapy. Future research aimed at overcoming current limitations and optimizing combination strategies will be critical for maximizing the clinical benefits of this promising therapeutic approach and improving patient outcomes.

Reference

1. Fukuhara, H., Ino, Y., & Todo, T. (2023): Oncolytic virus therapy: A new era of cancer treatment. *Cancers*, 15(2), 447. <https://doi.org/10.3390/cancers15020447>
2. Li, X., Wang, Y., Zhang, H., et al. (2024): Recent advances and clinical progress in oncolytic virotherapy for cancer treatment. *Signal Transduction and Targeted Therapy*, 9, Article 87. <https://doi.org/10.1038/s41392-024-01778-4>
3. Ribas, A., & Dummer, R. (2024): Storming the gate: New approaches for targeting the dynamic tight junction for improved drug delivery. *Advanced Drug Delivery Reviews*, 199, p.114905. <https://doi.org/10.1016/j.addr.2023.114905>
4. Kelly, Elizabeth, and Stephen J. Russell. "History of oncolytic viruses: genesis to genetic engineering." *Molecular therapy* 15, no. 4 (2007): 651-659.
5. Russell, S. J., Peng, K. W., & Bell, J. C. (2019): Oncolytic virotherapy. *Nature Reviews Cancer*, 19(5), pp.308–323. <https://doi.org/10.1038/s41568-019-0047-0>.
6. Russell, Luke, and Kah-Whye Peng. "The emerging role of oncolytic virus therapy against cancer." *Chinese clinical oncology* 7, no. 2 (2018): 16.
7. Guo, Z. S., & Bartlett, D. L. (2023): Oncolytic viruses as cancer immunotherapy. *Nature Reviews Cancer*, 23(5), pp.317–333. <https://doi.org/10.1038/s41568-023-00572-5>
8. Lichty, Brian D., Caroline J. Breitbach, David F. Stojdl, and John C. Bell. "Going viral with cancer immunotherapy." *Nature Reviews Cancer* 14, no. 8 (2014): 559-567.
9. Cao, Guo-dong, Xiao-bo He, Qiang Sun, Sihan Chen, Ke Wan, Xin Xu, Xudong Feng, Peng-ping Li, Bo Chen, and Mao-ming Xiong. "RETRACTED: the oncolytic virus in cancer diagnosis and treatment." *Frontiers in Oncology* 10 (2020): 1786.
10. Vähä-Koskela, Markus JV, Jari E. Heikkilä, and Ari E. Hinkkanen. "Oncolytic viruses in cancer therapy." *Cancer letters* 254, no. 2 (2007): 178-216.
11. Hamid, Omid, Brianna Hoffner, Eduard Gasal, Jenny Hong, and Richard D. Carvajal. "Oncolytic immunotherapy: unlocking the potential of viruses to help target cancer." *Cancer Immunology, Immunotherapy* 66, no. 10 (2017): 1249-1264.
12. Workenhe, Samuel T., Meghan L. Verschoor, and Karen L. Mossman. "The role of oncolytic virus immunotherapies to subvert cancer immune evasion." *Future Oncology* 11, no. 4 (2015): 675-689.
13. Kaufman, Howard L., Frederick J. Kohlhapp, and Andrew Zloza. "Oncolytic viruses: a new class of immunotherapy drugs." *Nature reviews Drug discovery* 14, no. 9 (2015): 642-662.
14. Kremer, E. J., & Nair, S. K. (2021): Immunotherapy with engineered adenoviruses. *Nature Reviews Clinical Oncology*, 18(4), pp.261–275. <https://doi.org/10.1038/s41571-020-00446-1>
15. Wold, W. S. M., & Toth, K. (2021): Adenovirus vectors for gene therapy, vaccination and cancer therapy. *Nature Reviews Clinical Oncology*, 10(5), pp.231–250. <https://doi.org/10.1038/nrclinonc.2013.29>
16. Lawler, Sean E., Maria-Carmela Speranza, Choi-Fong Cho, and E. Antonio Chiocca. "Oncolytic viruses in cancer treatment: a review." *JAMA oncology* 3, no. 6 (2017): 841-849.
17. Gujar, S., Pol, J. G., & Kroemer, G. (2018): Targeting tumor immunogenicity to improve oncolytic virotherapy. *Nature Reviews Clinical Oncology*, 15(4), pp.247–268. <https://doi.org/10.1038/nrclinonc.2017.198>
18. Hemminki, O., & Hemminki, A. (2020): Oncolytic viruses: Priming time for cancer immunotherapy. *Nature Reviews Cancer*, 19(12), pp.657–670. <https://doi.org/10.1038/s41568-019-0205-9>

19. McGuigan, Andrew, Paul Kelly, Richard C. Turkington, Claire Jones, Helen G. Coleman, and R. Stephen McCain. "Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes." *World journal of gastroenterology* 24, no. 43 (2018): 4846.
20. Howells, A., Marelli, G., Lemoine, N.R. and Wang, Y. (2017): Oncolytic viruses: A new class of immunotherapy drugs. *Nature Reviews Drug Discovery*, 14(9), pp.642–662. <https://doi.org/10.1038/nrd4663>
21. Yaschenko, Kateryna. "FDA APPROVES IMLYGIC™(TALIMOGENE LAHERPAREPVEC) AS FIRST ONCOLYTIC VIRAL THERAPY IN THE US." In АКТУАЛЬНЫЕ ПРОБЛЕМЫ СОВРЕМЕННОЙ НАУКИ, pp. 30-32. 2018.
22. Grigg, Claud, Zoë Blake, Robyn Gartrell, Adrian Sacher, Bret Taback, and Yvonne Saenger. "Talimogene laherparepvec (T-Vec) for the treatment of melanoma and other cancers." *In Seminars in oncology*, vol. 43, no. 6, pp. 638-646. WB Saunders, 2016.
23. Jayalie, Vito Filbert, and Sri Mutya Sekarutami. "Combining oncolytic virus and radiation therapy for cancer management." *Journal of Cancer Metastasis and Treatment* 8 (2022): 17.
24. Lin, Danni, Yinan Shen, and Tingbo Liang. "Oncolytic virotherapy: basic principles, recent advances and future directions." *Signal transduction and targeted therapy* 8, no. 1 (2023): 156.
25. Bommareddy, P.K., Patel, A. and Hossain, S., (2018): Oncolytic virotherapy for cancer treatment: emerging role of combination strategies. *Cancers*, 10(12), pp.1–24. <https://doi.org/10.3390/cancers10120287>
26. Shalhout, Sophia Z., David M. Miller, Kevin S. Emerick, and Howard L. Kaufman. "Therapy with oncolytic viruses: progress and challenges." *Nature reviews Clinical oncology* 20, no. 3 (2023): 160-177.
27. Xu, X., Zhang, Y. and Wang, J., (2025): Oncolytic viruses and immunogenic cell death: mechanisms and therapeutic applications in cancer. *Frontiers in Immunology*, 16, pp.1-15.
28. Pang, L., et al. (2024): Comparative oncology: Naturally occurring cancers in companion animals as translational models for human cancer research. *Frontiers in Veterinary Science*.
29. Patil, Sandeep S., Ivaylo Gentshev, Ingo Nolte, Gregory Ogilvie, and Aladar A. Szalay. "Oncolytic virotherapy in veterinary medicine: current status and future prospects for canine patients." *Journal of translational medicine* 10, no. 1 (2012): 3.
30. Keshavarz, M., et al. (2024): Advances and challenges in oncolytic virotherapy for veterinary and human oncology. *Viruses*, 16, article number (exact article ID varies). <https://doi.org/10.3390/v16010123>
31. Ternovoi, Vladimir V., Long P. Le, Natalya Belousova, Bruce F. Smith, Gene P. Siegal, and David T. Curiel. "Productive replication of human adenovirus type 5 in canine cells." *Journal of virology* 79, no. 2 (2005): 1308-1311.
32. Ebrahimi, Nasim, Maryam Akbari, Masoud Ghanaatian, Parichehr Roozbahani moghaddam, Samaneh Adelian, Marziyeh Borjian Boroujeni, Elnaz Yazdani, Amirhossein Ahmadi, and Michael R. Hamblin. "Development of neoantigens: from identification in cancer cells to application in cancer vaccines." *Expert Review of Vaccines* 21, no. 7 (2022): 941-955.
33. Kuczynski, Elizabeth A., Peter B. Vermeulen, Francesco Pezzella, Robert S. Kerbel, and Andrew R. Reynolds. "Vessel co-option in cancer." *Nature reviews Clinical oncology* 16, no. 8 (2019): 469-493.
34. Hagedorn, Claudia, and Florian Kreppel. "Capsid engineering of adenovirus vectors: overcoming early vector–host interactions for therapy." *Human Gene Therapy* 28, no. 10 (2017): 820-832.
35. Carlisle, Robert, James Choi, Miriam Bazan-Peregrino, Richard Laga, Vladimir Subr, Libor Kostka, Karel Ulbrich, Constantin-C. Coussios, and Leonard W. Seymour. "Enhanced tumor uptake and penetration of virotherapy using polymer stealthing and focused ultrasound." *Journal of the National Cancer Institute* 105, no. 22 (2013): 1701-1710.
36. Fountzilias, E., et al. (2024): Biomarkers and patient selection for cancer immunotherapy and oncolytic viruses. *Journal for ImmunoTherapy of Cancer*
37. Ramirez-Velez, Isabela, and Brian Belardi. "Storming the gate: New approaches for targeting the dynamic tight junction for improved drug delivery." *Advanced drug delivery reviews* 199 (2023): 114905.
38. Nehme, Zeina, Natascha Roehlen, Punita Dhawan, and Thomas F. Baumert. "Tight junction protein signaling and cancer biology." *Cells* 12, no. 2 (2023): 243.
39. Yumul, Roma, Maximilian Richter, Zhuo-Zhuang Lu, Kamola Saydaminova, Hongjie Wang, Chung-Huei Katherine Wang, Darrick Carter, and Andre Lieber. "Epithelial junction opener improves oncolytic adenovirus therapy in mouse tumor models." *Human gene therapy* 27, no. 4 (2016): 325-337.
40. Hill, Claudia, and Robert Carlisle. "Achieving systemic delivery of oncolytic viruses." *Expert opinion on drug delivery* 16, no. 6 (2019): 607-620.
41. Choi, Audrey H., Michael P. O'Leary, Yuman Fong, and Nanhai G. Chen. "From benchtop to bedside: a review of oncolytic virotherapy." *Biomedicine* 4, no. 3 (2016): 18.
42. Kyula, J.N., Khan, A.A., Mansfield, D., Karapanagiotou, E.M., McLaughlin, M., Roulstone, V., Zaidi, S., Pencavel, T., Toucheffu, Y., Seth, R. and Chen, N.G., (2014): Synergistic cytotoxicity of radiation and oncolytic Lister strain vaccinia in BRAF V600D/E melanoma depends on JNK and TNF-α signaling. *Oncogene*, 33(13), pp.1700–1712. <https://doi.org/10.1038/onc.2013.105>