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REVIEW ARTICLE

Updated oncolytic viruses for the treatment of bladder cancer: a systematic review

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ABSTRACT

Background and Objectives: Bladder cancer (BCa) is the most prevalent malignancy of the urinary tract and is often diagnosed at a late stage. Recurrence remains a major challenge for current treatment strategies. Over the past decade, the antitumor potential of oncolytic viruses (OVs) has been increasingly recognized, with several studies evaluating their safety and efficacy in BCa treatment. In this systematic review, we present clinical trials and animal studies to comprehensively evaluate the safety and therapeutic efficiency of various OVs in BCa.

Materials and Methods: After receiving the PROSPERO registration code, four electronic databases PubMed, Web of Science, Scopus, and Embase, were systematically searched to identify studies evaluating the safety and treatment potential of OVs in BCa. Two reviewers independently conducted the screening process, and data from clinical trials and animal studies were systematically extracted into Excel for subsequent synthesis and reporting. All steps of this systematic review adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions, upholding high standards of methodological rigor and transparency.

Results: The initial search strategy yielded 1,061 records. After removing duplicates, 809 articles were screened for relevance. Following the exclusion of 761 studies, 48 were deemed eligible for data extraction, comprising 17 clinical trials and 29 animal studies. Various oncolytic viruses were investigated, either as monotherapies or in combination with other agents, including Vaccinia virus, Adenovirus, Oncolytic adenovirus ONYX, Coxsackievirus A21 (CVA21), oncolytic CVA21 (V937), attenuated measles virus (MV-NIS virus), recombinant adenovirus (rAd), and a serotype 5 adenovirus engineered to express GM-CSF. All studies reported their most effective doses administered within safe parameters.

Conclusion: The common virus was the non-replicative recombinant adenovirus serotype 5 (Ad5), which encodes human interferon alfa-2b (IFNα2b) a cytokine with anti-tumor properties. It is administered via intravesical instillation and has received FDA approval.

Keywords: Bladder tumors; Oncolytic viruses; Urology

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INTRODUCTION

Bladder cancer (BCa) encompasses a spectrum of malignant tumors arising from the urothelium and, less commonly, other cellular components of the urinary bladder wall. It ranks among the most common cancers global, with an projected 614,298 new BCa patients and 220,596 deaths reported globally in 2022, making it the ninth most frequently diagnosed malignancy overall and the sixth most common in men (1). The predominant histological subtype is urothelial carcinoma (UC), formerly referred to as transitional cell carcinoma), which comprises approximately 90-95% of all bladder cancer diagnoses in developed countries. Rare histological subtypes include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and sarcoma, each of which carries distinct biological behavior, prognostic implications, and therapeutic considerations (2). BCa is broadly classified into two clinically and prognostically distinct categories and the depth of tumor invasion into the bladder wall forms the basis for classifying bladder cancer into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (3). BCa is broadly classified into NMIBC (stages 0 and I) and MIBC (stages II–IV). NMIBC is further stratified into low, intermediate, and high-risk disease according to the risk of recurrence and progression. Management strategies for MIBC are guided by disease stage, with distinct therapeutic approaches for stage II, stage III, and stage IV bladder cancer (4, 5).

The standard treatment for BCa, particularly NMIBC, includes transurethral resection of bladder tumor (TURBT) followed by intravesical therapy (IVT). This typically includes Bacillus Calmette-Guérin (BCG), which is the basis of NMIBC management. Despite a response rate of approximately 60% with BCG immunotherapy, there is currently no widely regarded gold standard for salvage intravesical therapy following adequate BCG treatment (6, 7).

Risk factors causing bladder cancer, smoking, chemicals, infectious agent's parasite schistosomiasis, and viruses, Human papillomavirus associated viruses (e.g., BK virus, and JC virus) seem to be in charge of the poor progression of BCa (8).

Various strategies have been proposed to enhance the efficacy of BCG immunotherapy or to provide rescue intravesical therapy following BCG treatment failure. Among them, oncolytic viruses (OVs) represent a novel and promising immunotherapeutic approach for cancer treatment, including BCa. These viruses selectively infect and destroy tumor cells through oncolysis, releasing newly formed infectious virions that further target residual cancer cells. Both naturally occurring and genetically engineered OVs demonstrate tumor-specific lytic activity while sparing healthy, non-tumoral tissues. Oncolytic herpes simplex was investigated in bladder cancer therapy (9).

This systematic review aims to represent findings from clinical trials and animal studies investigating the use of OVs in BCa treatment, while also highlighting current challenges and future research directions.

MATERIALS AND METHODS

The study protocol was prospectively registered in PROSPERO (Registration No. CRD42022345388) and was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022345388 (10).

Articles were retrieved from four key databases: PubMed, Scopus, Web of Science, and Embase. No filters or restrictions were applied during the search process. The search syntax and free-text terms were developed using resources from the MeSH Browser and the PubMed PubReMiner tool, which assist in analyzing term combinations. The search strategy was evaluated according to the Peer Review of Electronic Search Strategies (PRESS) guidelines (11). The search terms included a combination of ("Oncolytic Viruses" OR "oncolytic virotherapy" OR "Oncolytic*") AND ("Bladder malignancies" OR "Bladder tumor" OR "Bladder neoplasm" OR "bladder cancer" OR "Bladder*". To ensure inclusion of the most up-to-date research, the database search was updated using the same strategy in December 2024. Additionally, an expanded search was conducted by tracking both forward and backward citations of the studies included in our review in the Scopus database, thereby identifying additional potentially eligible articles or reports. As a final step, we manually screened the reference lists of relevant reviews found during our search to identify any additional studies. This review encompassed both randomized controlled trials (RCTs) evaluating oncolytic virus therapy for bladder cancer (BCa) and preclinical animal studies assess-

ing the therapeutic potential of genetically engineered and naturally occurring oncolytic viruses.

Study selection. The results of the literature search were imported into the EndNote library, where duplicate records were identified and removed. Two independent reviewers (HGH and RD) screened the titles and abstracts of all retrieved records to identify potentially eligible studies. Inter-reviewer agreement was assessed using Cohen's kappa coefficient, which demonstrated excellent agreement ($\kappa = 0.87$). Full-text articles of studies considered potentially eligible were subsequently retrieved and assessed for final eligibility and data extraction.

Data collection process. A data extraction form was developed and pilot-tested on five randomly selected studies by two reviewers (FKH and SMKA) to assess inter-rater reliability. The agreement was re-evaluated using Cohen's kappa, yielding a score of 0.95, which indicates near-perfect concordance. Following the resolution of any discrepancies, the reviewers independently extracted data. The extracted information was cross validated for inconsistencies, which were addressed through further discussion and consultation with a third reviewer.

The data encompassed study identifiers and design elements, including study name, location, dates, study design, type of virus, type of cancer, follow-up period, and main conclusions. For animal studies, additional variables such as virus type and animal model were documented.

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS), and scoring was performed for each study. The same two reviewers independently evaluated bias risk across relevant domains—classified as low, unclear, high, or not applicable—with justifications provided. Final decisions were confirmed in collaboration with a third reviewer (12). Each study was independently reviewed by the same two authors, who provided documented evidence and rationale to assess risk of bias across predefined domains (classified as low, unclear, high, or not applicable). Final decisions were reached through consensus with a third reviewer.

RESULTS

The search strategy yielded 1061 records, and after duplicate removal, 788 with an additional 21 found after updating the search in December 2024 (Fig. 1). A total number of 809 records underwent initial screening (title/abstract review). After the exclusion of 761 studies, forty-eight studies were considered suitable for data extraction, including 17 clinical trials and 29 animal studies.

Clinical trials investigating oncolytic viruses (OVs) for muscle-invasive bladder cancer (MIBC) began in 2001, initially focusing on the vaccinia virus's safety, lymphocyte recruitment, and induction of local inflammatory responses (Table 1). Multiple viral platforms have since been explored, including Vaccinia Virus, Adenovirus, ONYX Oncolytic Adenovirus, Coxsackievirus A21 (CVA21), V937 (oncolytic CVA21), MV-NIS (attenuated measles virus), Recombinant Adenovirus (rAd), and serotype 5 adenovirus engineered to express GM-CSF.

While most trials were conducted in the USA, other nations—such as Germany, Finland, Canada, UK, and Japan—also examined OV efficacy in BCa. Patient cohorts primarily included those with non-muscle-invasive bladder cancer (NMIBC), though several studies also targeted subgroups such as cystectomy candidates, recurrent carcinoma in situ (CIS), Ta/T1 disease, BCG-unresponsive NMIBC, and advanced solid tumors refractory to standard therapies.

Both monotherapy and combination therapy approaches were explored. Adjuvants included glucocorticoids, low-dose mitomycin C (MMC), cyclophosphamide, Pembrolizumab, and n-dodecyl-β-D-maltoside (DDM). Across studies, OVs demonstrated promising safety and efficacy profiles, primarily through modulation of the immune system. For instance, the Vaccinia virus showed safe intravesical administration with robust lymphocyte recruitment and inflammatory activation. SCH 58500, combined with a transduction-enhancing agent, was reported as safe, feasible, and biologically active in BCa patients. SCH 58500 is a replication-deficient recombinant adenovirus (serotype 5) engineered to carry and deliver the wild-type p53 tumour suppressor gene (also designated rAd/p53) directly into cancer cells via intravesical instillation.

CG0070 exhibited minimal toxicity following both single-dose and multidose intravesical administration (weekly and every four weeks), mirroring the tolerability of Ad5/3-D24-GMCSF. CG0070 is a selectively replicating (oncolytic) recombinant adenovirus that carries the human granulocyte-macrophage col-

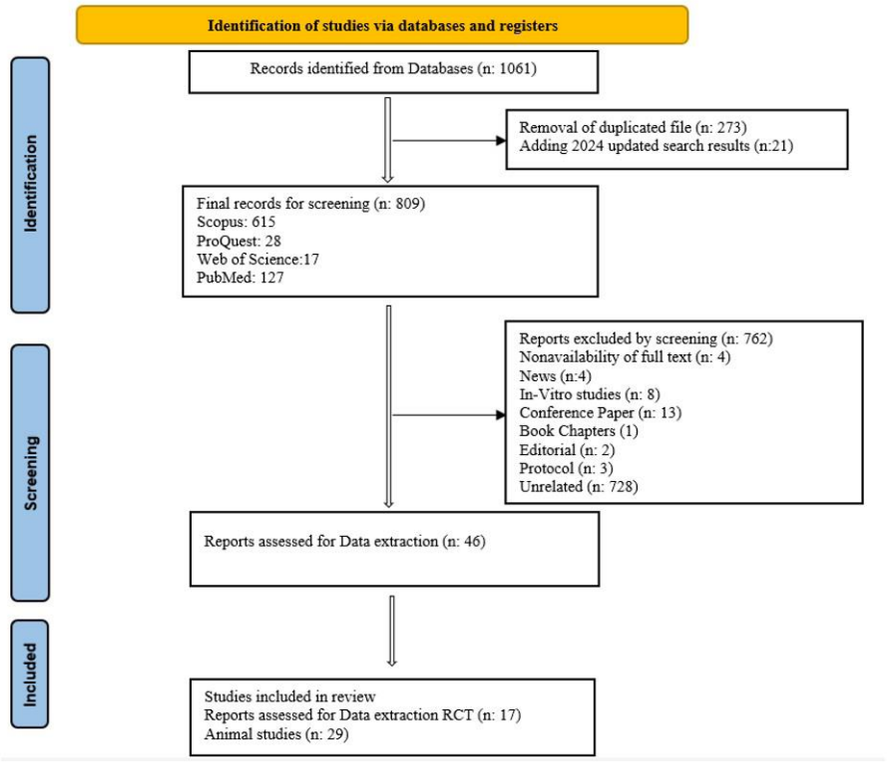

Fig. 1. A Prisma flow chart outlining the systematic review process, from recruiting articles to the final step of data extraction.

ony-stimulating factor (GM-CSF) transgene. It was developed by Cold Genesys, Inc. and is distinguished from earlier gene therapy agents by its ability to selectively replicate within and destroy tumour cells rather than simply delivering a gene payload. Adjuvant glucocorticoid therapy—with or without low-dose cyclophosphamide—appeared safe, and CG0070 showed strong response rates and limited disease progression in patients with pure CIS.

The clinical activity of CVA21 was evidenced by complete tumor response, viral replication, and virus-induced tumor inflammation. The investigational product CAVATAK demonstrated immunogenic tumor death and enhanced "immunological heat" within the tumor microenvironment, supporting its role as a novel therapeutic for NMIBC.

Promising results were also observed for CG0070 plus Pembrolizumab, repeated MV-NIS doses, and V937 with Pembrolizumab, each demonstrating favorable antitumor efficacy and tolerable safety. Studies also confirmed the significance of coxsackie adenovirus receptor expression and E2F promoter activity in OV-mediated treatment.

On December 16, 2022, the FDA approved Adstiladrin (nadofaragene firadenovec-vncg) for adult patients with BCG-unresponsive NMIBC presenting with CIS, with or without papillary tumors. This approval was based on NCT02773849, a multicenter, single-arm clinical trial enrolling 157 patients, including 98 evaluable cases of BCG-unresponsive CIS (Table 2).

A total of 29 animal studies, conducted between 1997 and 2023, demonstrated the antitumor efficacy of oncolytic viruses (OVs) against bladder cancer (BCa) (Table 3). These studies were conducted across various countries, including the USA, Canada, Taiwan, Japan, UK, China, Italy, Korea, and Germany, predominantly utilizing BALB/c nude mice bearing either human bladder cancer cells or MB49 xenograft models.

The collective evidence supports the therapeutic potential of OVs for both invasive bladder cancer and NMIBC. Many studies focused on the design and deployment of urothelium-specific adenoviral vectors, laying a foundation for bladder tumor-targeted OV therapies.

Genetically engineered oncolytic viruses include replication-defective adenoviral vectors (e.g., ADV/RSV-β-gal, rAd-Hras Rz, E1-deleted K1–5-encoding Ad), promoter- and tumor-specific adenoviruses (Ad-

Table 1. Detailed information of Clinical trials investigating oncolytic viruses (OVs) against BCa.

	First Author	Country	Year	NTC code	Study Phase	Tumor Type	Oncolytic Virus	Source of Virus	In Combination with	Number of Patients	Doses/TCID50	Follow up	Results
1	Leonard G. Gomella	Pennsylvania	2001	N/A	I	MIBC	Vaccinia Virus	Vaccinia Virus	-	4	The highest doses (100×10^6 PFU)	4 years	Intravesical delivery of the vaccinia virus has been shown to be well tolerated, promoting lymphocytic recruitment and the activation of a pronounced local inflammatory response in the BCa microenvironment.
2	Jürgen Kuball	Germany	2002	N/A	N/A	Cystectomy Candidate	SCH 58500 (rAd/p53)	Adenovirus	-	3	At cystoscopy at one dose level (7.5×10^{11} particles)	30 months	Intravesical administration of SCH 58500 in combination with a transduction-enhancing agent has been demonstrated to be safe, feasible, and capable of eliciting measurable biological activity in patients with BCa
3	John J Nemunaitis	USA	2009	N/A	I	Recurrent CIS, Ta, or T1	CG0070	Oncolytic adenovirus ONYX	-	13	Intravesical single dose CG0070 up to 3×10^{13} schedule at the first dose level (1×10^{12} viral particles)	-	Intravesical CG0070 exhibited a favorable tolerability profile following both single- and multiple-dose administration. Single doses of up to 3× 1013 viral particles were associated with limited local and systemic toxicity, while repeated dosing 1× 1012 viral particles weekly and then every four weeks maintained acceptable safety and demonstrated preliminary signs of therapeutic activity.
4	Anniina Koski	Finland	2010	N/A	N/A	Patients with advanced solid tumors that were unresponsive to standard therapeutic interventions	Ad5/3-D24-GMCSF	Oncolytic adenovirus	Low-dose metronomic cyclophosphamide	1/21	Intratumorally and intravenously with Ad5/3-D24-GMCSF,	74 Days	Ad5/3-D24-GMCSF is safe in BCa patients and exhibited preliminary evidence of therapeutic efficacy.
5	Maria Rajecki	Finland	2010	N/A	N/A	NMIBC	Oncolytic adenoviruses	Oncolytic adenovirus	Glucocorticoids and cyclophosphamide	14	(50 mg/daily or single 1000 mg intravenously)	2 months	The administration of glucocorticoids in BCa patients treated with oncolytic adenovirus therapy, either alone or in combination with low-dose cyclophosphamide, appears to be safe and well tolerated
6	James M Burke	USA	2012	N/A	I	NMIBC	CG0070	Oncolytic a denovirus	0.1% dodecyl maltoside	35	Intravesical infusions of CG0070 at 1 of 4 dose levels (1×10^{12}, 3×10^{12}, 1×10^{13} or 3×10^{13} viral particles)	10.4 months	Intravesical CG0070 was associated with a tolerable safety profile and anti-bladder cancer activity.
7	Nicola E Annels	UK	2016	NCT02316171	I/II	NMIBC	CAVATAK	Coxsackievirus A21 (CVA21)	Low-dose mitomycin C (MMC)	16	Step 1: Cohort 1 includes 3 BCa patients, received single CVA21 administration at 1×10^8 and Cohort 2 includes 3 BCa patients 3×10^8 TCID50 . In Cohort 3 the 3 BCa patients received two doses 3×10^8 TCID50 . Step 2: Same treatment of step 1 but both in combination with MMC (10mg).	30 days from the last dose	CVA21 demonstrated preliminary clinical activity, as indicated by complete BCa responses, evidence of intratumoral viral replication, and the induction of a notable inflammatory response associated with viral activity.
8	Vignesh T. Packiam. (13)	USA/Canada	2017	NCT02365818	II	BCG-unresponsive non–MIBC	CG0070	Oncolytic adenovirus	-	45	A fixed dose of 1×10^{12} viral particles	6 months	Pure CIS was associated with improved treatment response and limited disease progression
9	Nicola E Annels	UK	2019	NCT02316171	I	NMIBC	CAVATAK	Coxsackievirus A21 (CVA21)	Mitomycine	15	CVA21 (3×10^8 TCID50)	30 days from last dose	CAVATAK exhibited an acceptable safety profile in NMIBC.
10	Roger Li	Canada	2021	NCT04387461/ (CORE-001 trial)	II	BCG-unresponsive CIS with or without concurrent Ta or T1 disease	CG0070	Oncolytic adenovirus	Pembrolizumab	35	Intravesical CG0070 (1×10^{12} viral particles)	12 months	Promising safety and efficacy of CG0070 plus pembrolizumab in BCG-unresponsive NMIBC

Table 1. Continuing ...

11	Tanner, Miest	USA	2021	NCT03171493	I	Cystectomy Candidate and Ineligible for Neoadjuvant Cisplatin-based Chemotherapy	Attenuated MV-NIS virus	attenuated MV-NIS virus	-	8	Safe at a dose of 1×10^{11} TCID50	30 days after cystectomy	MV-NIS repeat dosing before RC is being assessed for safety and efficacy. Prior systemic safety at a dose of 1×1011 TCID50 data support the tolerability of intravesical administration
12	Stephen A Boorjian	USA	2022 (FDA approval)	NCT02773849	III	BCG-refractory and recurrent NMIBC	(rAd-IFNa/Syn3)	Adenovirus	=	103	Single-dose intravesical nadofaragene firadenovec (3×10^{11} vp/mL)	12 months	Nadofaragene achieved 49% bladder preservation, with favorable 5-year OS and cystectomy-free survival outcomes in CIS and papillary cohorts
13	Charles M Rudin	UK.	2023	NCT02043665	I	Urothelial Cancer BCG-unresponsive	oncolytic coxsackievirus A21 (V937)	oncolytic coxsackievirus A21 (V937)	Pembrolizumab	5 vs 46	DLT-guided dose escalation: 1×10^8, 3×10^8, and 1×10^9 TCID∞.	18.3 months (range, 1-175)	V937/pembrolizumab was well tolerated; despite intratumoral viral presence, clinical benefit did not exceed pembrolizumab monotherapy.
14	Robert S. Svatek	USA	2024	NCT04452591 (PIVOT-006/ (BOND-003)	III	NMIBC	Cretostimogene + DDM	oncolytic adenovirus	DDM (n-dodecyl-B-D-maltoside)	115/450	Cretostimogene (1×10^{12} virus particles) will be delivered via IVE after 5% DDM instillation.	52 months	Beneficial in recurrence-free survival (RFS), safety, tolerability, PFS, and time to subsequent intervention. Also, the quality of life (QoL) and immunogenicity markers improve
15	Neal D. Shore	USA	2017	NCT01687244 Gene therapy	II	NMIBC are either refractory to bacillus Calmette-Guerin (BCG) treatment	(rAd-IFNa/Syn3)	Recombinant adenovirus (rAd)	-	43	Intravesical rAd–IFNα/Syn3, randomized 1:1 to 1×10^{11} or 3×10^{11} vp/mL	12 months	The 12-month high-grade recurrence-free status.
16	Mark Tayson	USA	2020 /ongoing	NCT04452591/	III	BCG unresponsive patients with CIS±Ta/T1 to test CG	Cretostimogene Grenadenorepvec/ CG3002S	A serotype 5 adenovirus which was made to express GM-CSF	n-dodecyl-B-D-maltoside	115	Cretostimogene (1×10^{12} vp, IVE) administered following 5% DDM instillation	36 months	Primary: Overall complete response rate. Secondary: 12-month complete response rate, PFS, and safety
17	Chris Tosone	USA	2024	NCT04752722	I/II	NMIBC with CIS in patients who are either BCG-unresponsive or BCG-naïve/inadequately treated	EG-70/EG-70-101/ detalimogene voraplasmid)	EG-70 is a novel, investigational, non-integrating, non-viral gene therapy	-	14	Intravesical EG-70 (50 mL, 60-min dwell); 12-week cycles with either 2 doses (Days 1, 8) or 4 doses (Days 1, 8, 29, 36).	3 years	CR rate: 67% (14 patients) at Week 12; Phase III evaluation is needed to confirm efficacy.

Table 2. A comparative table showing the key features of Adstiladrin (nadofaragene firadenovec-vncg) versus other innovative intravesical therapies like CG0070 and Ad5/3-D24-GMCSF for BCG-unresponsive non-muscle invasive bladder cancer (NMIBC).

Feature	Adstiladrin (Nadofaragene Firadenovec)	CG0070	Ad5/3-D24-GMCSF
Vector Type	Non-replicating Adenovirus	Oncolytic Adenovirus	Oncolytic Adenovirus
Target Mechanism	IFN-α2b gene transfer	E2F-1 promoter → selective lysis + GM-CSF	Tumor-selective replication + GM-CSF
Immune Activation	Local cytokine stimulation (IFN-α)	Tumor lysis + GM-CSF-induced immunity	GM-CSF-enhanced immune response
Administration Route	Intravesical	Intravesical	Intravesical
Dosage Schedule	Every 3 months	Weekly for 6 weeks; maintenance varies	3 weekly doses + possible cycles
Complete Response Rate (CIS)	~51%	~47%	Data from Phase I/II trials
Median Duration of Response	~9.7 months	~6.5–10 months (study-dependent)	Under investigation
Adverse Effects	Spasms, urgency, fatigue, chills	Dysuria, urgency, flu-like symptoms	Fever, discomfort
FDA Approval Status	Approved (2022)	Phase III trials ongoing	Investigational (early-phase trials)

Table 3. Detailed information of both genetically engineered and wild-type OVs against the animal model of BCa.

	Year	First Author	Country	Cell line	Animal model	Vector detail	Conclusion
1	1997	Sutton, M. A. (USA)	USA	MBT-2 cells	murine model	Replication-defective adenovirus carrying the β-galactosidase gene under the Rous sarcoma virus (RSV) promoter.	ADV/RSV-tk with GCV demonstrates efficient gene transfer in vitro and effective therapy
2	1999	A Irie	USA	EJ human bladder carcinoma cells harboring a point mutation in H-ras.	nude mice	denovirus-mediated anti-H-ras ribozyme (rAd-Hras Rz)	Ribozyme-encoding adenovirus shows efficacy in experimental gene therapy of human BCa.
3	2001	Cozzi, P. J.	Canada	Poorly differentiated human TCC cell lines: J82, SK-UB, and T24.	An orthotopic syngeneic model	G207 is an engineered oncolytic HSV based on wild-type virus, and NV1020 is a clonal derivative of R7020 developed for HSV-1/HSV-2 vaccine research	Intravesical G207 and NV1020 demonstrated tumor-selective cytolysis and safety in an immunocompetent orthotopic bladder cancer model, with further studies required to define mechanisms and immune effect
4	2002	Jane Zhang	California	Bladder TCC (RT4, SW780), non-bladder cancer lines (G361, LNCaP, PA-1, U118), and primary human cells (lung fibroblasts, bladder smooth muscle, mammary epithelium).	BALB/c nu/nu mice carrying s.c. human TCC xenografts.	An Ad5 vector engineered with this promoter to control E1A/E1B expression, producing the attenuated replication-competent virus CG8840	CG8840 significantly inhibited RT4 xenograft growth in nude mice via intratumoral or i.v. administration, with synergistic tumor regression when combined with docetaxel. Results support UPII promoter–driven urothelium-specific adenoviral vectors for bladder cancer virotherapy.
5	2003	J-L Hsieh	Taiwan	Bladder cancer cells with mutant p53 (J82, TCC-SUP) versus those retaining wild-type p53 (TSGH-8301, BFTC-905).	–10-week-old female BALB/cByJ SmnPrkdc SCID mice used for TCC-SUP tumor implantation were sourced from the National Cheng Kung University Laboratory Animal Center	Ad5WS1 (E1B-55 kDa–deleted adenovirus) was constructed as described previously, and the E1-deleted Ad vector encoding K1–5 (Ad/K1–5) was generated as described	mUPII-like promoter activity enables urothelium-specific expression. E1B-19 kDa–deleted OVoffer enhanced lytic, BCa specific activity and, with a favorable therapeutic index and chemotherapy synergy, represent promising low-toxicity cancer therapies.
6	2004	Erich G. Hanel	Canada	Orthotopic bladder tumor model	Rat	Human reovirus selectively lyses cancer cells as an oncolytic virus.	Intravesical reovirus was safe and effective in preclinical bladder cancer models, indicating clinical potentia
7	2005	Kohno, S. I.	Japan	T24 and MBT-2 cells.	Immunocompetent mouse models.	Oncolytic herpes simplex virus (HSV) type 1 mutant HF10	Oncolytic HSV-1 strain HF10 is a promising candidate for superficial bladder cancer therapy.
8	2006	Wang, H.	Japan	Several cell lines (YTS-1, YTS-3, T24, J82, 5637)	SCID mouse model of orthotopic bladder cancer	AxdAdB-3 is a double-restricted oncolytic adenovirus with mutant E1A and E1B-55 kDa deletion.	AxdAdB-3 intravesical therapy demonstrates promising efficacy for bladder cancer
9	2007	Ai-Li Shiau	Taiwan	MBT-2 bladder tumor cells showed in vitro lysis of HER-2/neu–overexpressing human, murine bladder, and hamster oral cancer cells.	Mice	A conditionally replicating, gE-deficient PrV expressing HSV-1 gD and thymidine kinase under the HER-2/neu promoter.	YP2 demonstrates therapeutic potential in invasive bladder cancer and, given HER-2/neu overexpression across cancers, may have broader oncologic utility
10	2011	Justin C. Paglino	USA	T24	Immunodeficient homozygous CB17-SCID mice	VSV-G/GFP expresses native G and a G–GFP fusion (inserted between G and L genes).	VSV is a promising oncolytic agent for mesodermal tumors, with interferon modulators overcoming resistance to oncolysis
11	2012	Simpson, G. R.	UK	Bladder carcinoma lines (EJ, T24, RT112, VM-CUB1, TCCSUP-G, 5637, KU-19-19), plus BHK-21 and AY-27 cells.	Fischer F344 female rats	OncovexGALV/CD, an oncolytic herpes simplex virus-1	OncovexGALV/CD demonstrates improved local tumor control in bladder cancer and may modulate disease progression in preclinical models
12	2012	Fang Wang	China	EJ cells	subcutaneous xenografts tumor in nude mice	Bladder-specific oncolytic adenoviruses APU-E1A and APU-E1A-AR (PSCAE-UPII-E1A–based constructs)	APU-E1A-AR and APU-E1A intratumoral administration was well tolerated in mice without effects on health or behavior
13	2013	Conghui Han	China	MB29 bladder tumors	Intratumoral injection was performed in syngeneic C57BL/6 mice and nude mice bearing	PPE3-SEA is a tumor-specific oncolytic adenovirus expressing SEA, with E1A/E1B regulated by hTERT and HIF promoters.	PPE3-SEA is a promising oncolytic adenovirus platform for SEA delivery and bladder cancer treatment

Table 3. Continuing ...

					EJ ($CD40^+$) bladder cancer xenografts.		
14	2014	Parviainen, S.	Finland	Bladder cancer cells (EJ, CD40þ)	Intratumoral injection was performed in syngeneic C57BL/6 mice and nude mice bearing EJ ($CD40^+$) bladder cancer xenografts.	an oncolytic vaccinia virus expressing hCD40L (vvdd-hCD40L-tdTomato)	CD40L-expressing oncolytic vaccinia virus mediates antitumor activity via lysis, apoptosis induction, and Th1 immune activation
15	2015	Kwan Joong Joo	USA	MBT-2 cells	in C3H/He mice	HSV-2–based oncolytic virus targeting Ras-activated tumor cells	HSV-2–based oncolytic virus demonstrates potent bladder cancer activity via direct lysis and tumor-specific immune activation, supporting its potential as an intravesical therapy
16	2015	Lu, C. S. Aldo	Taiwan	TCC-SUP cells (5×10^6)	NOD/SCID mice	AdLCY: adenoviral vector encoding the adenylyl cyclase (ADCY/LCY) transgene	AdLCY targets hypoxic bladder tumors and CSCs and may represent a broader Oct4-linked anticancer strategy across cancers
17	2016	Pourchet Kyle	USA	MBT2 cells (5×10^5)	female C3H/HeN	Herpes simplex virus-1 (HSV-1) evades CD8+ T-cells by producing ICP47	TAP inhibitor–armed oncolytic viruses can evade $CD8^+$ T-cell detection and trigger robust local and systemic antitumor immunity
18	2017	G Potts	Canada	Primary human bladder cancer explants	orthotopic immunecompetent AY-27	A vaccinia virus (VACV)–based oncolytic construct with F4L gene mutation targeting the viral RRM2 homolog	F4L-deleted vaccinia viruses showed replication in bladder cancer explants with improved safety and selectivity, supporting their potential in BCG-refractory disease
19	2018	Nicola E. Annels	UK	MB49/ICAM-1 cells treated with or without CVA21	C57BL/6 mice orthotopic	CVA21 is an intercellular adhesion molecule-1 (ICAM-1)–targeted immunotherapeutic virus	CVA21 immunotherapy represents a potentially safer, more efficacious option for bladder cancer
20	2018	Cheng Hu	China	UM-UC-3 cells (2.5×10^6 cells)	MIBC BALB/c-nu/nu mice	Alphavirus M1 selectively targets bladder cancer cells without affecting normal cells	Oncolytic virus M1 shows targeted therapeutic potential in MIBC
21	2018	Anton Oseledchyk	USA	The murine bladder cancer cell line for melanoma (MB49)	C57BL/6J mice	Newcastle Disease Virus (NDV)	NDV intratumoral therapy combined with systemic immunomodulators is a promising strategy independent of tumor lysis sensitivity
22	2019	Eva Lichtenegger	Germany	UMUC3	athymic nude mice	The oncolytic, YB-1 selective adenovirus XVir-N-31	XVir-N-31 delivered intratumorally under ultrasound guidance effectively delayed tumor growth, demonstrating practical targeted delivery
23	2020	Keigo Iizuka	Japan	TCC-NU1	Immunodeficient nude mice	Recombinant measles virus (rMV-SLAMblind)	rMV-SLAMblind shows promise as a virotherapy for canine TCC
24	2021	Ying Liu	China	NC UM-UC-3 cells or sh CCDC6 UM-UC-3 cells	Female BALB/c-nu/nu mice	M1 virus	Defines a mechanistic target for developing compounds that improve oncolytic virotherapy efficacy
25	2022	Coby Rangsitratkul,	Canada	MB49	C57Bl/6 mice	Novel oncolytic vesicular stomatitis virus containing the human GM-CSF transgene (VSVd51-hGM-CSF)	VSVd51-hGM-CSF shows promise as a viro-immunotherapy for BCa
26	2022	Yun-Hui Jeon	Korea	MB49	C57BL/6 and BALB/c mice	Oncolytic vaccinia virus (VACV; JX-594, pexastimogene devacirepvec)	Oncolytic VACV induces durable antitumor immunity, evidenced by long-lived, tumor-specific $CD8^+$ T cells capable of proliferating in response to dendritic cell antigen presentation
27	2023	Che-Yuan Hu	Taiwan	Murine MBT-2 bladder cancer cell line	C3H/HeN mice	A Clec4a2 shRNA-expressing oncolytic adenovirus derived from Ad.LCY	Ad.shDCIR is a promising combinatorial viro-immunotherapy candidate for bladder and other cancers
28	2023	Woodson W. Smelser	USA	MBT2 urothelial bladder cancer	orthotopic syngeneic C3H murine model	Oncolytic reovirus plus + anti-PD-1	Intravesical reovirus, anti–PD-1, or their combination improved survival in a murine bladder tumor model, driven by MDSCs and $CD8^+$ T-cell–mediated immune effects
29	2023	Andrea Vannini	Italy	MDAMB-468, MCF-7, SK-BR-3, A-431, BxPC-3, CAPAN-1, SK-OV-3, MDA- MB-231, PANC-1, HPAC, U-251, U-2-OS, HeLa, K-562 (No BCa cell lines)	C57BL/6 and BALB/c mice	R-421, an innovative retargeted onco-immunotherapeutic herpesvirus	Nectin4-retargeted oncolytic herpesvirus demonstrates proof-of-concept efficacy as a strategy for hard-to-target cancers

5WS1, AxdAdB-3, APU-E1A, APU-E1A-AR, PPE3-SEA, Ad9OC, XVir-N-31), as well as engineered herpes simplex viruses (G207, HF10, HSV-2 OV), human reovirus, recombinant measles virus (rMV-SLAM-blind), a modified vaccinia virus (F4L-mutant VACV), and vesicular stomatitis virus expressing human GM-CSF (VSVd51-hGM-CSF).

DISCUSSION

Clinical trials investigating oncolytic viruses in humans have evaluated a variety of agents, either as standalone therapies or in combination regimens. These include naturally occurring and genetically modified viruses such as *Vaccinia virus*, wild-type, and oncolytic strains of *Adenovirus* (e.g., ONYX), *Coxsackievirus* A21 (CVA21) and its oncolytic derivative V937, MV-NIS virus, and recombinant *adenoviruses* (*rAd*). Among these, the most frequently utilized was a replication-deficient recombinant *adenovirus* serotype 5 (*Ad5*) encoding *human interferon alfa-2b* (*IFNα2b*), a cytokine with established anti-tumor activity. This construct, administered via intravesical instillation, has received FDA approval, with all studies identifying optimal therapeutic doses administered within safe clinical parameters.

The CG0070 targets *retinoblastoma* (*Rb*) pathway-defective cells, common in BCa, and expresses GM-CSF to enhance immune activation. It is delivered intravesically (directly into the bladder). And currently in Phase 3 trials for high-risk BCG-unresponsive NMIBC alone or in combination with pembrolizumab (KEYTRUDA®) to amplify immune response (14). Earlier Phase 2 trials (e.g., BOND2) showed encouraging complete response rates in patients who refused cystectomy (13, 15). A program is available in the U.S. for eligible patients who are BCG-unresponsive. Monotherapy complete response rates of around 62% have been reported in earlier trials. Combination with pembrolizumab is being studied due to its potential for synergistic immune activation.

SCH 58500 (*rAd/p53*) is a recombinant *adenoviral* vector designed to deliver the wild-type p53 tumor suppressor gene into cancer cells. It is typically administered via intravesical instillation or intraperitoneal injection, depending on tumor location. It was developed by Schering-Plough (later acquired by Merck) as a gene therapy approach for various malignancies, including BCa. SCH 58500 aims to restore functional p53 in tumor cells, promoting apoptosis and inhibiting proliferation (16). Clinical development entered Phase 2/3, but the program was discontinued. SCH 58500 was also investigated in head and neck cancers, ovarian cancer, and gliomas (17). A Phase I study in BCa patients receiving intravesical SCH 58500 showed successful p53 transgene expression in 7 of 8 assessable patients after intravesical instillation.

Ad5/3-D24-GMCSF is a genetically engineered oncolytic adenovirus designed to selectively replicate in and terminate cancer cells. It stimulates antitumor immunity through the expression of GM-CSF. As an *armed* oncolytic virus, it combines direct tumor lysis with immune system activation, enhancing the therapeutic impact. Intravesical administration has demonstrated a favorable safety profile, with minimal systemic toxicity. In early-phase clinical trials, up to 83% of patients achieved radiological disease control, and 50% exhibited partial or minor responses, highlighting the potential for treating BCa (18). Across Phase I studies of *Ad5/3 D24 GM CSF* in advanced solid tumors, 83% of patients achieved radiologic disease control (CR + PR + SD) and about 50% showed partial or minor responses (18).

CAVATAK is a CVA21-based oncolytic immunotherapy targeting ICAM-1 and DAF overexpressed in bladder cancer, showing promise in NMIBC (19). Anti–PD-1 and anti–CTLA-4 show synergistic effects in preclinical models, enhancing tumor control and reducing recurrence (20-22). CAVATAK activates innate and adaptive immunity, increasing IFN-response genes, PD-L1, LAG-3, and Th1 chemokines (23). During a Phase I study with 15 NMIBC patients, both monotherapy of intravesical CAVATAK alone and in combination with low-dose mitomycin C to enhance ICAM-1 expression, resulting in induced tumor inflammation and hemorrhage. Phase I NMIBC data showed intravesical CAVATAK, alone or with low-dose mitomycin C, induced tumor inflammation and hemorrhage via ICAM-1 upregulation (23).

The MV-NIS virus, a genetically modified measles virus encoding the sodium iodide symporter (NIS), has shown promising results as an oncolytic therapy for bladder cancer, particularly in patients with urothelial carcinoma who are ineligible for standard chemotherapy. It can be administered directly into

the bladder via a catheter, and dosing includes either a single instillation or two doses spaced two weeks apart (24-26). The *MV-NIS* virus can be well tolerated with minimal adverse events (only one case of mild hematuria) (27).

Adstiladrin (nadofaragene firadenovec), an adenoviral gene therapy, was approved in 2022 for high-risk BCG-unresponsive NMIBC with CIS ± papillary lesions (28). This represents the first approved adenoviral vector–based gene therapy and the first gene therapy authorized for bladder cancer. Efficacy was evaluated in the CS-003 (NCT02773849) multicenter, single-arm trial involving 157 patients with high-risk NMIBC, including 98 with BCG-unresponsive CIS. Patients received intravesical nadofaragene firadenovec-vncg (75 mL, 3×10^{11} vp/mL) every three months for up to one year or until toxicity or high-grade recurrence, with responders allowed continued dosing at three-month intervals (29). At 3 months after treatment, 50 patients achieved complete response, with 46% maintaining response for ≥12 months and a median duration of response of 9.7 months. Common adverse events included instillation-site discharge, fatigue, bladder spasms, urinary urgency, hematuria, chills, fever, and dysuria. Approval of nadofaragene firadenovec provides a new therapeutic option for BCG-unresponsive NMIBC with CIS, particularly for patients unsuitable for cystectomy (29).

Among patients with NMIBC receiving BCG therapy, researchers examined whether human *cytomegalovirus* (*HCMV*) reactivation increases treatment outcomes. In a cohort of 90 individuals, 47 patients (52%) tested positive for *CMV*, and this group showed significantly longer recurrence free survival (HR 0.58 [0.35–0.97], p = 0.039). Approximately half of the *CMV*-positive patients displayed adaptive NK cell populations, and these individuals experienced complete responses to BCG (p = 0.0002). In contrast, patients lacking adaptive NK cells had a markedly higher recurrence rate (p = 0.0002). The investigators concluded that HCMV leaves long lasting functional imprints on NK and T cells, which may alter the tumor microenvironment when the virus reactivates. Reactivation of HCMV after BCG treatment could therefore influence therapeutic outcomes and represents a potential immunologic target. Because HLA E plays a central role in NK cell checkpoint signaling, these findings support exploring therapies that block NKG2A (such as *monalizumab*) or strategies that boost $NKG2C^+$ adaptive NK cell responses, including adoptive NK cell therapies (30).

Preclinical studies using mouse models of BCa have been running to evaluate the safety, efficacy, and immune mechanisms of OVs. These models—especially BALB/c nude mice bearing human BCa xenografts or MB49 murine high-grade BCa cells—offer a controlled environment to test viral replication, tumor lysis, and immune activation (31-33). Li W. conducted a study investigating the synergy between oncolytic adenoviruses and Erastin, a strong inducer of ferroptosis. Their findings revealed that this combination markedly suppressed bladder tumor growth while avoiding significant toxicity. This innovative strategy may improve the therapeutic effectiveness of oncolytic virotherapy, particularly in resistant tumors, by leveraging ferroptosis pathways (34). Several challenges and limitations are considered in oncolytic virus treatment of bladder cancer, such as tumor delivery barriers, antiviral immunity, tumor heterogeneity, limited penetration into solid tumor masses, viremia safety concerns, and regulatory and manufacturing challenges.

CONCLUSION

Both randomized controlled trials (RCTs) and in vivo studies have demonstrated the safety and efficacy of OVs in the treatment of BCa. Among these, the most utilized OV in clinical trials is the non-replicative recombinant adenovirus serotype 5 (Ad5), engineered to deliver human interferon alfa-2b (IFNα2b), a cytokine with potent anti-tumor and immunomodulatory properties. Administered via intravesical instillation, this therapy has received FDA approval for the high-risk NIMIBC. The OVs are increasingly recognized as a promising modality for selectively targeting and lysing tumor cells. Moreover, accumulating evidence suggests that certain OVs can elicit robust anti-tumor immune responses, positioning them as dual-acting agents that combine direct oncolysis with immune stimulation.

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