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Wen-Jing Zeng , Yi-Fan Zeng , Li-Jun Zhou , Jing Yi , Sheng Deng , Zheng-Zheng Liu , Qian-Qian Ye *

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Article

The Efficacy and Safety of Oncolytic Viruses in Treatment of Glioma: A Meta-Analysis

Wen-Jing Zeng [1,2,3,†], Yi-Fan Zeng [4,†], Li-Jun Zhou [5], Jing Yi [6], Sheng Deng [1,2,3], Zheng-Zheng Liu [7] and Qian-Qian Ye [1,2,3,*]

[1] Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, Hunan, China
[2] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, China
[3] The Hunan Institute of Pharmacy Practice and Clinical Research, Xiangya Hospital, Central South University, Changsha, China
[4] Department of Cardiovascular Surgery, the Second Xiangya Hospital, Central South University, Changsha, Hunan, China
[5] Department of Pharmacy, Hainan Hospital of Chinese People's Liberation Army General Hospital, Sanya, China
[6] Department of Pharmacy, 331 Hospital, Zhuzhou, Hunan, China
[7] Department of Oncology, Xiangya Hospital, Central South University, Changsha, Hunan, China
* Correspondence: xyeqian@csu.edu.cn
† These authors contributed equally to this work.

Abstract: Objective: The main purpose of this meta-analysis was to assess the efficacy and safety of Oncolytic Viruses (OVs) in glioma therapy. **Methods:** We searched the literature in PubMed, EMBASE, Web of Science, and the Cochrane Library. The primary outcomes assessed were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events (AEs). The risk of bias was evaluated by sensitivity analysis and publication bias. **Results:** We identified 21 studies with 440 patients in this meta-analysis. In the single-arm analysis, the results showed that the 1-year OS rate was 47% (95% CI: 34%-61%, $I^2 = 75\%$) and the 2-year OS rate was 14% (95% CI: 10%-20%, $I^2 = 0\%$). The median OS was 12.48 months (95% CI: 10.71-14.25, $I^2 = 96\%$). The 1-year PFS rate was 13% (95% CI: 5%-24%, $I^2 = 0\%$), with the median PFS being 4.01 months (95% CI: 2.99-45.03, $I^2 = 96\%$). The pooled estimate of ORR was 7% (95% CI: 3%-12%, $I^2 = 23\%$). Funnel plots for median PFS were asymmetric with Egger's test $P < 0.01$ indicating publication exists. The incidence of OVs-related AEs was 49% (95% CI: 20%-79%, $I^2 = 95\%$), and AEs > grade 3 was 8% (95% CI: 3%-16%, $I^2 = 62\%$). **Conclusion:** This meta-analysis indicated that OVs therapy was relatively safe but did not significantly extend survival in patients with gliomas.

Keywords: glioma; oncolytic viruses; drug efficacy; drug safety; meta-analysis

1. Introduction

Gliomas represent the most prevalent malignant tumor of the central nervous system, comprising 49% glioblastomas (GBM) and 30% diffusely infiltrating low-grade gliomas (LGG) [1]. The CBTRUS Statistical Report illustrates that GBM exhibits a higher prevalence among adults compared to children, with incidence rates escalating with age, peaking in the 75-84 age bracket [2]. GBM is considered one of the most malignant forms of glioma and is characterized by a median survival time of approximately 8 months [2,3]. The standard treatment protocol, known as the Stupp regimen, involves maximal surgical resection of tumor tissue while preserving neural integrity, supplemented by radiotherapy and temozolomide chemotherapy, the latter being the primary chemotherapeutic agent for gliomas [4]. Nevertheless, the prognosis for gliomas remains dismal, with a mere 6.8% survival rate at the five-year mark post-diagnosis of GBM [2]. Advanced age, propensity

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for radiotherapy resistance, and incomplete tumor resection all serve as negative prognostic indicators for malignant gliomas [5].

Oncolytic viruses (OVs) are a novel class of tumor immunotherapeutic agents. These viruses, whether occurring naturally or genetically modified, exhibit a characteristic of selectively targeting tumor cells, thereby eliciting replication within tumor cells and subsequent tumor cell lysis [6]. Upon infecting tumor cells, OVs trigger various mechanisms including apoptosis, necrosis, and autophagy induction, thereby culminating in the destruction of the malignant cells [7]. This property renders OVs a highly promising modality in anti-tumor immunotherapy [8,9]. Following the FDA approval of the first OV drug, talimogene laherparepvec (T-VEC), for the treatment of advanced melanoma in 2015, clinical trials investigating OVs as monotherapies or in combination with other modalities have been initiated across a broad spectrum of cancers including gliomas, bladder, and colorectal cancers [10,11]. Notably, a modified herpes simplex virus (HSV) received approval for the treatment of brain cancers, such as GBM, in Japan in 2021. Numerous preclinical studies have reported promising outcomes, demonstrating significant anti-tumor activity of OVs against gliomas and a prolongation in survival in animal models [12–15]. However, the efficacy of OVs in improving the prognosis of gliomas in clinical trials remains controversial. Consequently, we conducted this meta-analysis to systematically assess the feasibility of OVs application in gliomas.

2. Materials and Methods

2.1. Search Strategy

We searched the Embase, PubMed, Web of Science, and Cochrane Library databases for literature published since the establishment of the database until August 2024, with no language restrictions. Keywords included “oncolytic virus”, “Virus, Oncolytic”, “oncolytic treatment”, “oncolytic adenovirus”, “oncolytic virotherapy”, “oncolytic immunotherapy”, and “oncolytic vaccine”, and “glioma” “glioblastoma”, “glial tumor”, “astrocytoma” “oligodendroglioma”, and “ependymoma”. The detailed search strategy was listed in the Supplementary Table S1.

2.2. Study Selection

We pre-registered this meta-analysis (PROSPERO ID: CRD42024577506) and utilized Covidence for study screening.

We included all clinical studies of patients with primary or recurrent glioma treated with oncolytic viruses. These studies can provide viral interventions (virus family, mode of administration, dose, duration of administration) and patient outcomes (overall survival (OS), progression-free survival (PFS), and objective response rate (ORR)). Studies were rejected if they meet the following criteria: (1) in vitro or animal experiments; (2) Viral interventions or patient outcomes are not available; and (3) case reports or conference abstract.

2.3. Data Extraction

Two authors independently screened the literature and then extracted data, with a third researcher overseeing the process. Any disagreements were resolved through group discussions.

The extracted data includes (1) Study characteristics: author, year, country, study phase, and number of participants; (2) Patient information: diagnosis, gender, and age; (3) Treatment strategy: viral family, delivery method, dose and duration, combination administration; (4) Primary clinical outcomes: OS, PFS, ORR, and AEs.

2.4. Quality Assessment

The Cochrane Risk of Bias Tool (ROB2) was used to evaluate the quality of randomized controlled trial (RCT), and NOS was used in retrospective cohort studies and prospective case-control studies.

2.5. Statistical Analysis

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All the analyses were performed by R (Version 4.4.1). Methods for evaluating heterogeneity include the Cochran Q test and I^2 statistics. The source of heterogeneity was investigated by subgroup analysis. Funnel plot, Egger's test, and Begg's test were conducted to evaluate publication bias. $P < 0.05$ meant that the difference was statistically significant.

3. Results

3.1. Studies Selection and Characteristics

As shown in Figure 1, we retrieved a total of 4348 articles in 4 databases and deleted 1688 duplicates. By sifting through the titles and abstracts of the articles, we removed 2540 irrelevant articles. The remaining 120 articles were surveyed by full-text reading and 99 articles were then excluded. Finally, 21 articles with 440 patients were included [16–36].

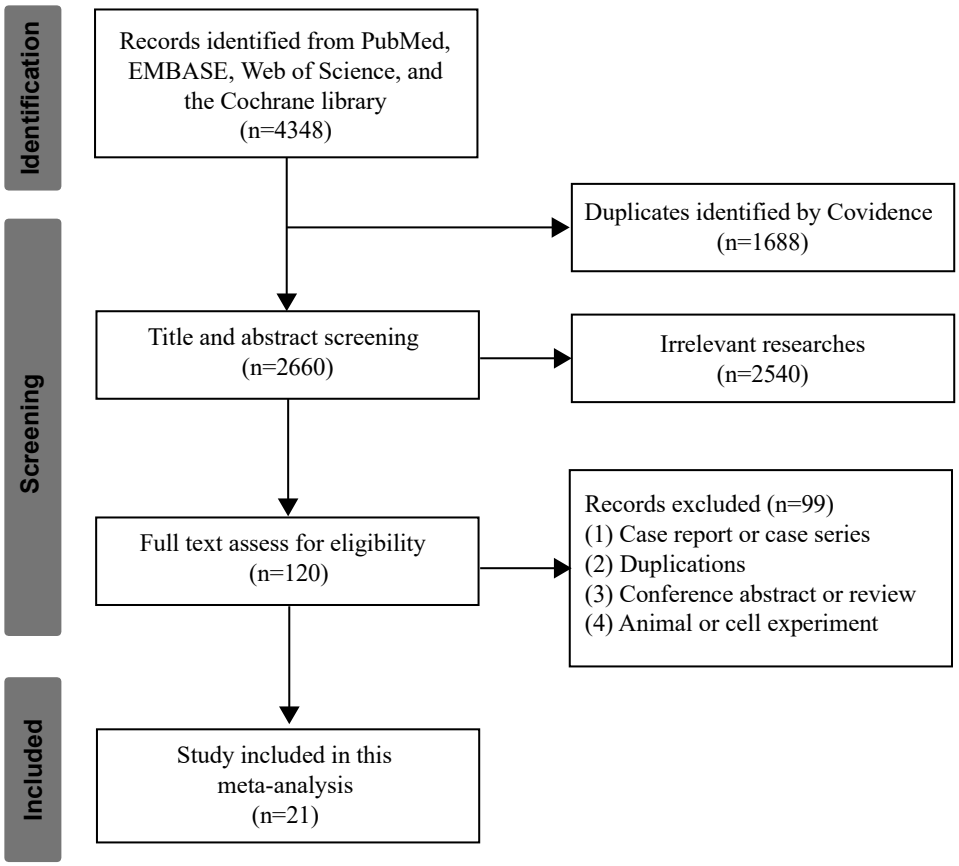

Figure 1. The PRISMA flow chart of this meta-analysis.

The detailed baseline characteristics of the included studies were shown in Table 1. This meta-analysis included 14 phase I studies, 2 phase II studies, and 5 phase I/II studies with publication years ranging from 2000 to 2024. Concerning the delivery method, 19 studies utilized intratumoral administration, and 2 studies utilized intravenous administration.

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Table 1. Baseline characteristic information of included research.

Author	Year	Country	Study design	N (M/F)	Age	Diagnose	Viral family	Delivery	Dose (duration)	Previous treatment	End Points
Chiocca [16]	2004	USA	Phase I	24 (17/7)	52 (35–70)	AA, AO, or GBM (Recurrent)	ONYX-015, E1B-attenuated adenovirus	I.T.	10^7 pfu inoculated into theresected tumor cavity	S: 24 RT:24 CT:24	OS, PFS
Desjardins [17]	2018	USA	Phase II (NCT01491893)	61 (25/36)	55 (20–75)	GBM (Recurrent)	PVSRIPO, polio–rhinovirus chimera	I.T.	10^7–10^10 (7 doses)	S: 61 RT: 61 CT: 61 BEV: 61	OS
Fares [18]	2021	UK	Phase I (NCT03072134)	12 (7/5)	52 (48–65)	AA or GBM (ND)	NSC-CRAd-S-pk7, adenovirus	I.T.	Corhort 1: 6.25 × 10^10 VP, Corhort 2: 1.25 × 10^11 VP, Cohort 3: 1.875 × 10^11 VP (1 dose)	S: 12	OS, PFS, ORR
Forsyth [19]	2008	USA	Phase I	12 (5/7)	53.5 (40–61)	AA, AO, or GBM (Recurrent)	Reovirus	I.T.	72h infusion of 10^7, 10^8, or 10^9 TCID50	S: 12 RT: 12 CT: 10	OS, PFS, ORR
Freeman [20]	2006	USA	Phase I/II	11 (5/6)	44.5	GBM (Recurrent)	NDV-HUJ, Newcastle disease virus	I.V.	Part 1: 0.1, 0.32, 0.93, 5.9, and 11 BIU; Part 2: 11 BIU	S: 10 Biopsy: 4 RT: 14 CT: 12	OS, PFS
Friedman [21]	2021	USA	Phase I (NCT02457845)	12 (6/6)	13.4 (7-18)	AA or GBM (Recurrent)	G207, HSV-1	I.T.	10^7-10^8 PFU	S: 12 RT: 12 CT: 12 BEV: 3	OS, PFS, ORR
Galanis [22]	2024	USA	Phase I/II (NCT00390299)	22 (11/11)	53.5 (37.0 - 69.0)	AA or GBM (Recurrent)	MV-CEA, carcinoembryonic antigen-expressing oncolytic measles virus	I.T.	2×10^6-2×10^7 PFU	CT: 22 BEV: 5	OS, PFS, ORR
Geletneky [24]	2017	USA	Phase I/IIa (NCT01301430)	18 (4/14)	57.8 ± 10.6	GBM (Recurrent)	ParvOryx, H-1 parvovirus (H-1PV)	I.T.	Arm1: 5×10^9 pfu; Arm2: 1×10^9 pfu	S: 18 RT: 18 CT: 18	OS, PFS
Kicielinski [25]	2014	USA	Phase I	15 (5/10)	51.52 (26.2 – 76.3)	GBM, GS, AA, anaplastic mixed glioma, or AO (Recurrent)	REOLYSIN, Reovirus	I.T.	1×10^8-1×10^10 pfu	S: 15 RT: 15 CT: 15	OS, PFS, ORR
Lang [26]	2018	USA	Phase I (NCT00805376)	group A: 25(10/15); group B: 12 (6/6)	group A: 52 (21-62), group B: 49 (29-60)	GBM, GS, or AA (Recurrent)	DNX-2401, adenovirus	I.T.	1×10^7–3×10^10 VP (1 dose)	S: 25 RT: 37 CT: 36	OS, PFS, ORR
Ling [27]	2023	USA	Phase I (NCT03152318)	41	56 (27-74)	GBM or HGG (Recurrent)	CAN-3110, HSV	I.T.	10^6–10^10 PFU	S: 38 RT: 41 CT: 41 BEV: 30	OS, PFS

 doi:10.20944/preprints202409.1161.v1

Markert [29]	2000	USA	Phase I	21 (14/7)	54.1 (38–72)	AA or GBM (Recurrent or progressive)	G207, HSV	I.T.	10^6-3×10^9 pfu injected over 2 min in 5 operative locations	S: 17 Biopsy: 4 RT: 21 CT: 10	OS, PFS
Markert [28]	2009	USA	Phase Ib (F05041106)	6 (4/2)	54.5 (39–65)	GBM (Recurrent)	G207, HSV	I.T.	1.5 × 10^8 pfu (2 doses)	S: 6 RT: 6 CT: 5	OS
Markert [30]	2014	USA	Phase I (NCT00157703)	9 (3/6)	50.4 (37–60)	AA or GBM (Recurrent)	G207, HSV	I.T.	1.0 × 10^9 pfu (1 dose)	S: 9 RT: 9 CT: 9	OS, PFS
Nassiri [36]	2023	Canada	Phase I/II (NCT02798406)	49 (20/29)	53 (26–73)	GBM or GS (Recurrent)	DNX-2401, adenovirus	I.T.	5 × 10^8, 5 × 10^9 and 5 × 10^10 VP	S: 4, RT: 49 CT: 49 BEV: 6	OS, ORR
Pérez-Larraya [23]	2022	USA	Phase Ia (NCT03178032)	12 (7/5)	9 (3-18)	DIPG (ND)	DNX-2401, adenovirus	I.T.	1×10^10 and 5×10^10 VP	/	OS, PFS, ORR
Samson [31]	2018	UK	Phase Ib (EudraCT: 2011-005635-10)	6	62 (45-66)	HGG (Recurrent)	REOLYSIN, Reovirus	I.V.	1×10^10 single dose	S: 6 RT: 6 CT: 6 BEV: 1	OS, PFS
Thompson [32]	2023	USA	Phase Ib (NCT03043391)	8 (3/5)	16.5 (11–18)	HGG (Recurrent)	PVSRIPO	I.T.	5 × 10^7	CT: 8 BEV: 2	OS
Todo [33]	2022	Japan	Phase I/II (UMIN000002661)	13 (5/8)	46 (35–76)	GBM (Recurrent)	G47Δ, HSV	I.T.	Cohort 1: 6 × 10^8 pfu, Corhort 2: 2 × 10^9 pfu	S: 13 RT: 13 CT: 13	OS, PFS, ORR
Todo [35]	2022	Japan	Phase II (UMIN000015995)	19 (4/15)	50.89 (25-73)	GBM (Residual or recurrent)	G47Δ, HSV	I.T.	1 × 10^9 pfu per dose (up to six doses)	S: 19 RT: 19 CT: 19 BEV: 7	OS, PFS, ORR
van Putten [34]	2022	USA	Phase I	20 (8/12)	53.5 (29–69)	GBM (Recurrent)	Delta24-RGD, adenovirus	I.T.	10^7–1×10^11 VP	S: 19 RT: 20 CT: 19 BEV: 6	OS, PFS

Notes: ND, newly diagnosed; I.T., intratumoral administration; I.V., intravenous administration; ADV, adenovirus; HSV, herpes simplex virus; NDV, newcastle disease virus. HGG, high-grade glioma; GBM, glioblastomas; AA, astrocytomas; AO, anaplastic oligodendroglioma; DIPG, diffuse intrinsic pontine glioma; GS, gliosarcoma; S, Surgery; RT, radiation therapy; CT, chemotherapy; BEV, bevacizumab; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

3.2. Overall Survival by Single-Arm Meta-Analysis

To explore the effect of OVs on OS in glioma patients, we pooled 21 articles containing 22 single-arm studies [16–36]. The forest plot showed that the median OS of glioma patients receiving OVs therapy was 12.43 months (95% CI: 10.65-14.21, $I^2 = 96\%$, $P < 0.01$) (Figure 2A). Subgroup analysis revealed recurrent glioma was an important source of heterogeneity in this meta-analysis (Table 2). The sensitivity analysis results of the median OS suggested that no studies should be ruled out (Figure 2B). The funnel plot for the median OS was symmetric and both Egger's test (P = 0.15) and Begg's test results exhibited no obvious difference (P = 0.76) (Figure 2C).

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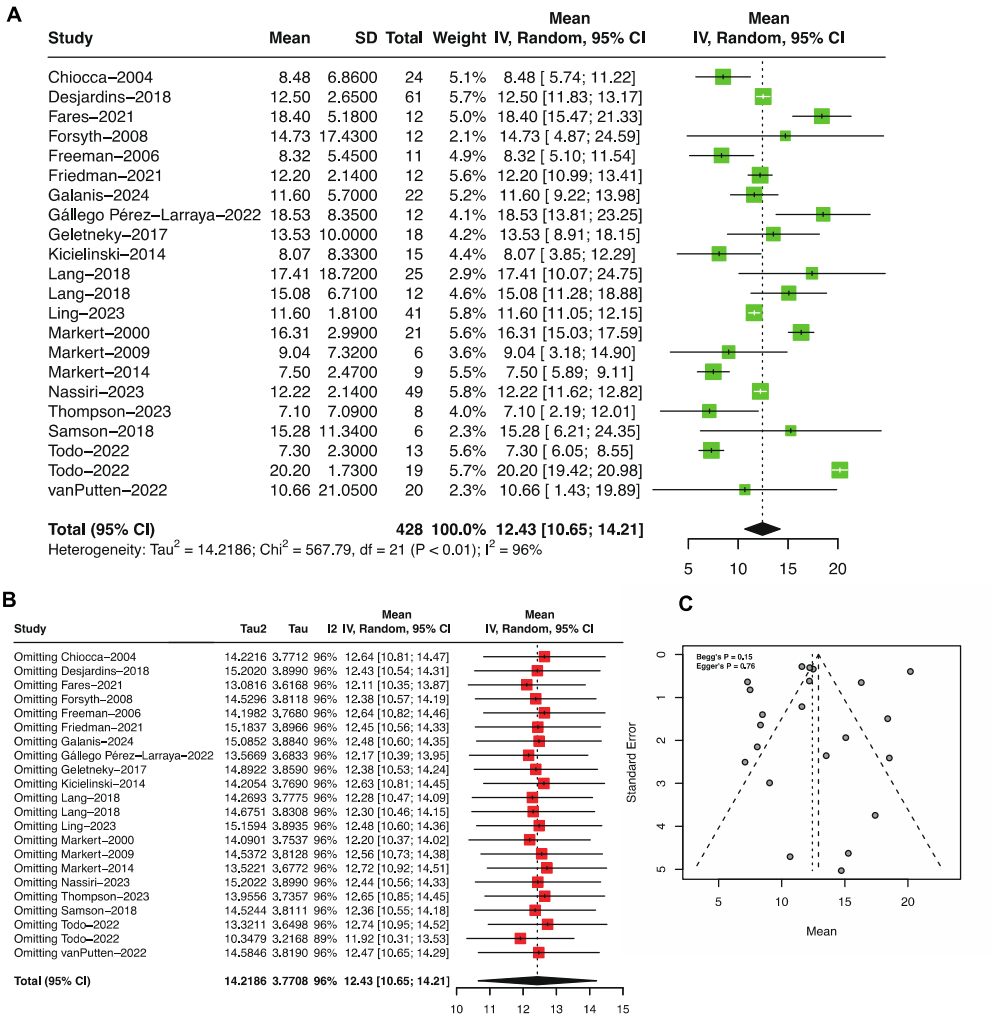

Figure 2. Overall survival of OVs in treatment of glioma. (A) The pooled estimate of median OS. (B) sensitive analysis of median OS. (C) funnel plot of median OS.

Table 2. Subgroup analysis of pooled estimates of the median overall survival.

Subgroup	No. of studies	Mean, months	95% CI	P value between subgroups	heterogeneity within subgroups	
					I^2 (%)	P value
Study Phase				0.21		
Phase I	15	12.50	10.31, 14.70		88	< 0.01
Phase I/II	2	10.40	8.07, 12.74		100	< 0.01
Phase II	5	16.35	8.80, 23.89		100	< 0.01
Diagnose				< 0.01		
ND	2	18.44	15.95, 20.93		0	0.96
Recurrent	20	11.82	10.07, 13.57		97	< 0.01
Administration				0.53		
I.T.	20	12.57	10.71, 14.44		97	< 0.01
I.V.	2	10.45	4.16, 16.74		50	0.16

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Viral family			0.25		
ADV	7	14.31	11.17, 17.45	83	< 0.01
HSV	7	12.16	8.53, 15.79	99	< 0.01
Reovirus	3	11.27	5.91, 16.63	33	0.22
Poliovirus	2	10.37	5.20, 15.54	78	0.03
NDV	1	8.32	5.10, 11.54	/	/
Measles virus	1	11.60	9.22, 13.98	/	/
Parvovirus	1	13.5	8.91, 18.15	/	/

Notes: ND, newly diagnosed; I.T., intratumoral administration; I.V., intravenous administration; ADV, adenovirus; HSV, herpes simplex virus; NDV, newcastle disease virus.

We further pooled the OS data at 1-year 14 studies [16–19,21–25,31,33–35] and 2-year (11 studies) [16–19,23–25,31,34–36] from glioma patients treated with OVs therapy. As shown in Figure 3, 1-year and 2-year OS rates for glioma patients were 47% (95% CI: 34%-61%, $I^2 = 75\%$, $P < 0.01$) and 14% (95% CI: 10%-20%, $I^2 = 0\%$, $P = 0.87$), respectively.

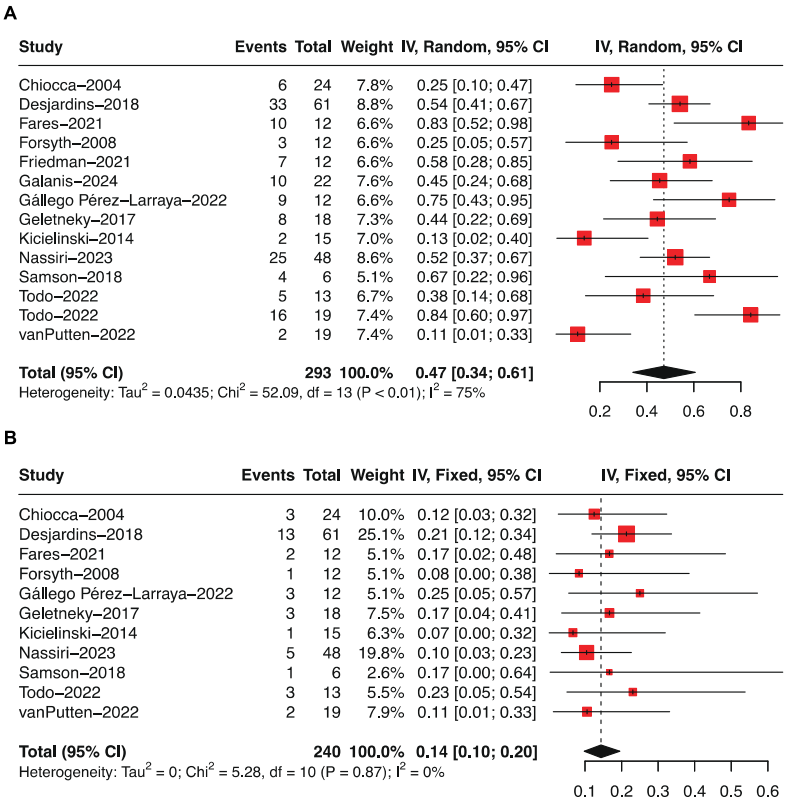

Figure 3. Forest plot showing the (A) 1-year and (B) 2-year overall survival of glioma patients treated with OVs.

3.3. Progression-Free Survival by Single-Arm Meta-Analysis

A subsequent analysis of PFS data from18 single-arm studies in 17 publications found that the median PFS of glioma patients receiving OVs therapy was 3.92 months (95% CI: 2.93-4.92, $I^2 = 95\%$, $P < 0.01$) (Figure 4A) [16,18–27,29–31,33–35]. Although no statistical difference, OVs showed a longer PFS in the treatment of newly diagnosed (ND) glioma (Table 3). Based on the sensitive analysis result of median PFS, no research needs to be ruled out (Figure 4B). The funnel plot for the median PFS was

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asymmetric with significant differences in Egger's test ($P < 0.01$) (Figure 4C) indicating publication exists.

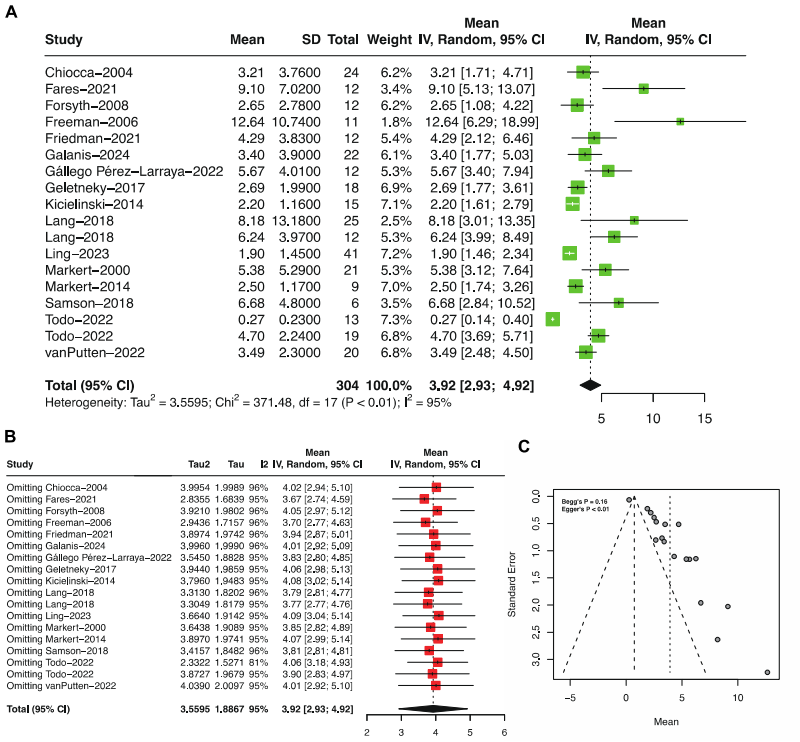

Figure 4. Progression-free survival of OVs in treatment of glioma. (A) The pooled estimate of median PFS. (B) sensitive analysis of median PFS. (C) funnel plot of median PFS.

Table 3. Subgroup analysis of pooled estimates of the median progression-free survival.

Subgroup	No. of studies	Mean, months	95% CI	P value between subgroups	heterogeneity within subgroups	
					I^2 (%)	P value
Study Phase				0.68		
Phase I	13	4.06	3.01, 5.12		80	< 0.01
Phase I/II	4	3.91	0.30, 8.12		94	< 0.01
Phase II	1	4.70	3.69, 5.71		95	< 0.01
Diagnose				0.05		
ND	2	6.98	3.71, 10.25		54	0.14
Recurrent	16	3.54	2.61, 4.47		96	< 0.01
Administration				0.06		
I.T.	16	3.59	2.66, 4.51		96	< 0.01
I.V.	2	9.10	3.36, 14.84		60	0.12
Viral family				0.25		
ADV	6	5.30	3.56, 7.05		70	< 0.01
HSV	6	2.99	1.42, 4.56		97	< 0.01
Reovirus	3	2.98	1.33, 4.63		62	0.07
NDV	1	12.64	6.29, 18.99		/	/

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Subgroup	No. of studies	Mean, months	95% CI	P value between subgroups	heterogeneity within subgroups	
					I^2 (%)	P value
Measles virus	1	3.40	1.77, 5.03		/	/
Parvovirus	1	2.69	1.77, 3.61		/	/

Notes: ND, newly diagnosed; I.T., intratumoral administration; I.V., intravenous administration; ADV, adenovirus; HSV, herpes simplex virus; NDV, newcastle disease virus.

One-year PFS data was also collected in 5 studies and the result showed the 1-year PFS rate was 13% (95% CI: 5%-24%, $I^2 = 0\%$, $P = 0.74$) (Figure 5) [18,21,23,25,31].

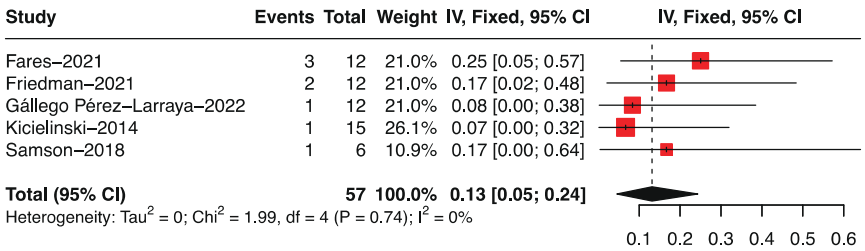

Figure 5. Forest plot showing the 1-year progression-free survival of glioma patients treated with OVs.

3.4. Objective Response Rate by Single-Arm Analysis

We then included 10 studies with 190 patients to evaluate the effect of OVs on ORR in glioma patients

To assess the effect of OVs on ORR in glioma patients, we included studies with 10 studies with 190 patients for analysis [18,19,21–23,25,26,33,35,36]. The pooled estimate of ORR was 7% (95% CI: 4%-12%, $I^2 = 33\%$, $P = 0.14$) (Figure 6).

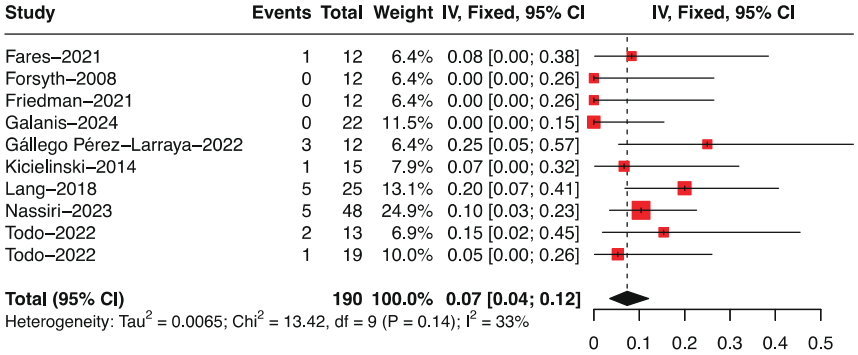

Figure 6. Forest plot showing the objective response rate of glioma patients treated with OVs.3.5 The Safety of OVs in the Treatment of Gliomas.

To evaluate the safety of OVs in the treatment of gliomas, we analyzed the OVs-related adverse events (AEs). In total, 9 studies with 233 patients were included in the analysis of AEs related to OVs [17,18,21–23,26,27,35,36], and 13 studies with 268 patients were included in the analysis of AEs > grade 3 [16–19,21–25,27,30,34,35]. The results showed that the incidence of OVs-related AEs was 49% (95% CI: 20%-79%, $I^2 = 95\%$, $P < 0.01$) (Figure 7A), and AEs > grade 3 was 8% (95% CI: 3%-16%, $I^2 = 62\%$, $P < 0.01$) (Figure 7B).

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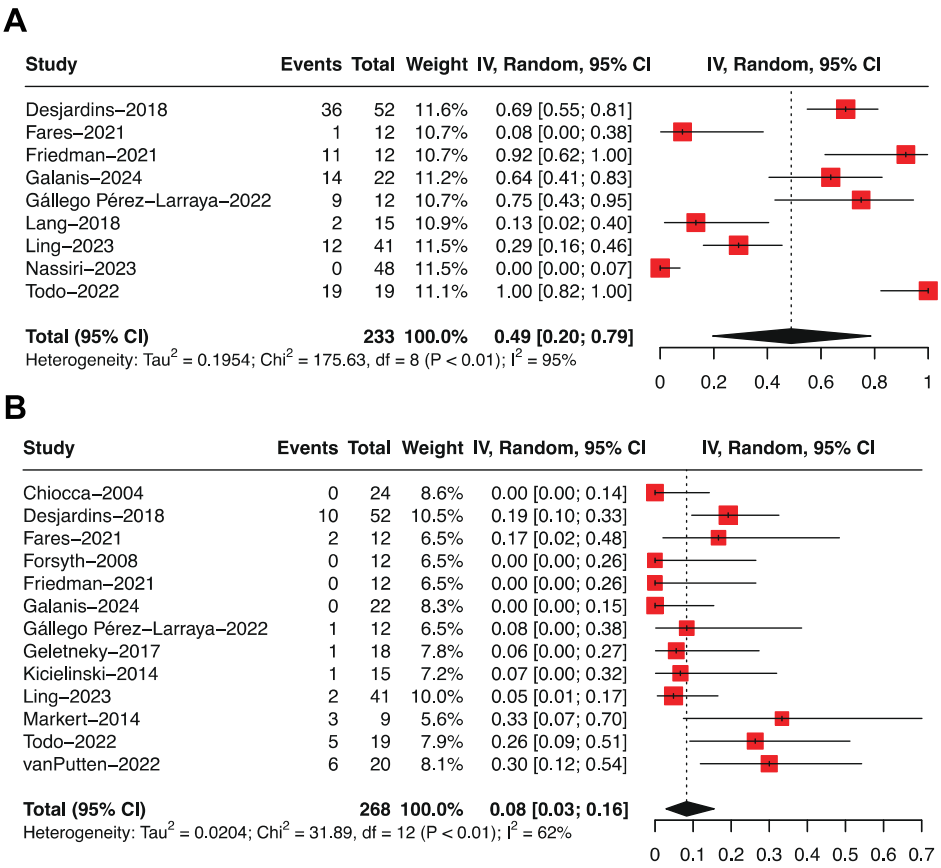

Figure 7. Forest plot showing the AEs (A) and AEs > grade 3 (B) of glioma patients treated with OVs.

4. Discussion

To assess the efficacy and safety of OVs in the treatment of gliomas, 21 articles with 440 patients were included in this meta-analysis. Our results revealed that OVs therapy did not prolong OS and PFS in this meta-analysis. In glioma patients treated with OVs, the incidence of AEs was 49%, and the incidence of AEs ≥ grade 3 was only 8%, suggesting that OVs were relatively safe in glioma.

The median OS and PFS in glioma patients treated with OVs therapy were 12.48 months and 4.01 months, respectively. A recently published meta-analysis delineated a median OS range from 7.2 to 16 months and a median PFS range from 5.1 to 12 months among patients with recurrent high-grade glioma undergoing re-irradiation combined with systematic therapy [37]. Notably, despite optimal treatment approaches, GBM patients typically exhibit a median OS of merely 12-15 months [38]. Furthermore, a prior investigation conducted by our research team established a median PFS of 3.72 months for PD-1/PD-L1 therapy in glioma patients [39]. These findings collectively suggested that OVs fail to confer a survival advantage in the context of gliomas management. Due to differences in the subtype, stage, and inherent heterogeneity of glioma, only a portion of glioma patients will eventually benefit from OVs treatment, so how to screen glioma patients for oncolytic virus therapy and select the appropriate oncolytic virus therapy for them is still a great challenge.

The tumor immune microenvironment, comprising glioma cells, various immune cells, and diverse chemokines and cytokines, has been implicated in the suboptimal efficacy of several immunotherapies [40,41]. Among the non-tumor cells within this milieu, tumor-associated macrophages (TAMs) are predominant, and the intricate interplay between TAMs and OV-infected tumors has been proposed as a significant factor contributing to the therapeutic ineffectiveness of

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OVs [42,43]. TAMs undergo polarization influenced by different microenvironmental factors and cytokines, displaying distinct phenotypic characteristics, conventionally categorized into M1 and M2 types [44]. M1 TAMs instigate a pro-inflammatory response, while M2 TAMs engage in an anti-inflammatory response, characterized by the expression of surface proteins following stimulation with interleukin-10 (IL-10) and transforming growth factor beta (TGF-β). Following administration of OVs, beyond direct tumor lysis, infected tumor cells release chemoattractants such as CCL2, which recruit macrophages and microglia to the injection site. This recruitment prompts polarization of TAMs towards the M1 phenotype, fostering an immune response against tumor proliferation [44,45]. Nonetheless, this cascade also triggers an antiviral response, thereby attenuating the therapeutic efficacy of OVs. During the lytic cycle of lysosomal virus infection, both innate and adaptive immunity are engaged, leading to rapid recruitment and activation of macrophages into virus-infected tumor cells. These polarized pro-inflammatory macrophages secrete chemokines and cytokines, activating other innate immune cells like natural killer cells and dendritic cells (DCs), thus bolstering the antiviral immune response and facilitating viral clearance via phagocytosis [46]. Additionally, TAM-induced secretion of TNF-α was observed to stimulate extracellular apoptotic pathways, substantially diminishing viral replication [47]. In vitro investigations have corroborated that TNF-α inhibitors markedly enhanced the overall efficacy of lysovirus therapy [48,49]. Furthermore, infected tumor cells exhibit heightened release of type I interferon, which not only impedes the intracellular viral life cycle but also augments the recruitment of antigen-presenting cells, dendritic cells, innate lymphocytes, and ultimately, tumor-specific cytotoxic T-lymphocytes [50,51].

Another challenge encountered in systemic administration of OVs is its limited diffusion ability within tumor tissues to effectively cross the blood-brain barrier. Additionally, systemic administration of OVs is vulnerable to neutralization by complement and antibodies, as well as early uptake by circulating macrophages, thereby further reducing the viral load that reaches glioma cells [52]. Among the 21 studies included in this meta-analysis, local administration was utilized for efficient virus transport, which encompassed intratumoral administration as well as convection-enhanced delivery (CED). Intratumoral administration, being the most commonly employed method, ensures localized high drug concentrations within the tumor. However, invasive procedures like CED, implantation in the residual cavity post-tumor removal, and other modalities present challenges in terms of repeated drug administration [53]. At present, various drug loading systems and delivery techniques are being explored to overcome the obstacles associated with gliomas drug delivery modalities. These approaches encompass nanoparticle modification, exosome modification, autologous mesenchymal stem cells, and others. Encouragingly, preclinical studies have demonstrated improved delivery outcomes [54–57]. We are eagerly anticipating and firmly believe that, in the near future, effective therapeutic concentrations within the brain can be achieved through systemic delivery or more convenient delivery methods, resulting in groundbreaking advancements in glioma treatment.

5. Conclusions

The OVs therapy is relatively safe but is not effective in extending the survival of glioma patients.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Search strategy in the different database.

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