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REVIEW

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The clinical utility of autologous tumor lysate-loaded dendritic cell vaccination for patients with glioma: A systematic review and meta-analysis

Mohammad Amin Habibi[1] | Mohammad Sina Mirjani[2] | Muhammad Hussain Ahmadvand[3] | Pouria Delbari[3] | Shayan Arab[4] | Poriya Minaee[2] | SeyedMohammad Eazi[2] | Sajjad Ahmadpour[5]

[1]Department of Neurosurgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2]Student Research Committee, Qom University of Medical Sciences, Qom, Iran

[3]Student Research Committee, Tehran University of Medical Sciences, Tehran, Iran

[4]School of Medicine, Islamic Azad University, Tehran Medical Branch, Tehran, Iran

[5]Patient Safety Research Center, Clinical Research Institute, Urmia University of Medical Sciences, Urmia, Iran

Correspondence
Sajjad Ahmadpour, Patient Safety Research Center, Clinical Research Institute, Urmia University of Medical Sciences, Urmia, Iran.
Email: sajjadahmadpour@yahoo.com

Abstract

Background: Dendritic cell (DC) vaccines show promise for glioma treatment, but optimal use remains uncertain. This meta-analysis examined DC vaccine efficacy and safety for gliomas.

Methods: This systematic review and meta-analysis study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. From the date of inception to October 23, 2023, electronic databases PubMed, Embase, Web of Science, and Scopus have been thoroughly evaluated.

Results: A total of 12 studies with 998 patients and a mean age ranging from 40.2 to 56 years were included. Across 12 articles, DC vaccine 6-month overall survival (OS) was 100% [95% confidence interval {95%CI}: 100%–100%]. Respectively, 12-month OS reported 75% [95%CI: 65%–85%] but declined to 32% [95%CI: 20%–43%] for 24-month OS. 6- and 12-month progression-free survival reached 49% [95%CI: 21%–77%] and 19% [95%CI:8%–30%]. Studying radiological outcomes shows that complete response and partial response rates were 13% [95%CI: 17%–42%], and 26% [95%CI: 10%–42%], though stable disease reached 33% [95%CI: 15%–51%], suggesting predominant antineoplastic effects. The progressive disease rate also was 24% [95%CI: 9%–57%].

Conclusions: In gliomas, DC vaccinations show a temporary efficacy; stability is more prevalent than regression. Impacts favor decreased resistance to early disease. Enhancing efficacy remains critical. Early therapy can be enhanced by appropriate supplementary therapy integration.

KEYWORDS
dendritic cell vaccine, GBM, glioma, immunotherapy

Abbreviations: CI, confidence interval; CR, complete response rate; DC, dendritic cell; GBM, glioblastoma; MOS, median overall survival; ORR, overall response rate; PD, progressive disease rate; PFS, progression-free survival; PR, partial response rate; SD, stable disease.

1 | INTRODUCTION

Dendritic cell (DC) vaccines loaded with tumor lysates have emerged as a promising immunotherapy approach for patients with malignant gliomas. Multiple clinical trials over the past two decades have evaluated the safety and efficacy of this therapeutic strategy.[1] conducted one of the first clinical studies showing that vaccination with autologous DCs pulsed with tumor lysates elicited antigen-specific cytotoxic T-cell responses in glioma patients. Since then, numerous phase I/II trials have further investigated DC vaccines in newly diagnosed and recurrent glioblastoma (GBM).[2–4] Recent research efforts have focused on identifying predictors of response and optimizing DC vaccine manufacturing and administration protocols. Molecular subgroup classification and B7-H4 expression levels correlate with vaccine response in GBM patients.[5] Combining DC vaccination with standard treatments like chemotherapy and radiation has also been explored as a synergistic therapeutic approach.[3–6]

The largest clinical trial to date, a multi-center randomized phase III study, demonstrated that adding a tumor lysate-pulsed DC vaccine to standard therapy improved overall survival (OS) in newly diagnosed GBM patients compared to standard therapy alone.[7,8] Other studies utilizing allogeneic glioma stem-like cell lysates or whole tumor lysate-pulsed DCs have also shown promising results.[9,10] However, a few trials have reported limited or no survival benefit with DC vaccines.[11,12] Further research is needed to determine the efficacy of this immunotherapeutic strategy conclusively.

This systematic review and meta-analysis aims to synthesize the current clinical evidence on tumor lysate-loaded DC vaccines for malignant gliomas. Specifically, we will evaluate the impact of DC vaccination on OS, progression-free survival (PFS), immune response measures, and adverse events. Subgroup analyses based on glioma type, grade, and prior treatments will also be conducted to identify patients most likely to benefit from DC vaccines. The results of this study can guide designing future clinical trials and assessing the potential for incorporating DC vaccines into the treatment options for malignant gliomas.

2 | METHOD

The preparation of this study strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[13]

2.1 | Search strategy

The search strategy employed keywords such as “glioma,” “glia tumor,” “epidermis dendritic cell,” “dendritic cell vaccine,” and “vaccines” to construct the search criteria for electronic databases. PubMed/Medline, Embase, and Scopus were systematically searched from their inception to October 23, 2023, without imposing restrictions on publication date, type, or language. The complete search syntax is provided in the supplementary files.

2.2 | Study selection process

Data from each electronic database were input into EndNote v.20. Following the removal of duplicate articles, two reviewers (Poriya Minaee and SeyedMohammad Eazi) independently conducted a two-step title/abstract screening to identify pertinent studies. A full-text assessment has been conducted to assess the studies that satisfy the eligibility criteria. A third senior reviewer (Mohammad Amin Habibi) supervised the confirmation of the study selection process.

2.3 | Eligibility criteria

We set a PICO (Patients, Intervention, Comparator, Outcome) platform for addressing the aim of the study: Patients with glioma, Intervention: Tumor lysate-loaded DC vaccine, Comparator: radiotherapy, chemotherapy, and other non-immunotherapy treatments, Outcome: OS, PFS, complications.

2.4 | Inclusion criteria

1. English studies
2. Clinical studies
3. Studies on patients with glioma
4. Patients received DCVax-L
5. Original studies of randomized and non-randomized clinical trials, cohorts, cross-sectional, case-control, and case series

2.5 | Exclusion criteria

1. Non-English studies
2. In vivo and in vitro studies
3. Studies on patients rather than with glioma
4. Patients received other platforms of DC vaccines
5. Case reports, review articles, book chapters, and letters to the editor without original findings

2.6 | Data extraction

Two reviewers conducted the data extraction of included studies independently, ensuring a thorough and reliable process. The information of studies was extracted, including name of author, year of publication, country, number of patients, mean age, gender of patients, follow-up time, grade of tumor, type of tumor, DC vaccine regimen,

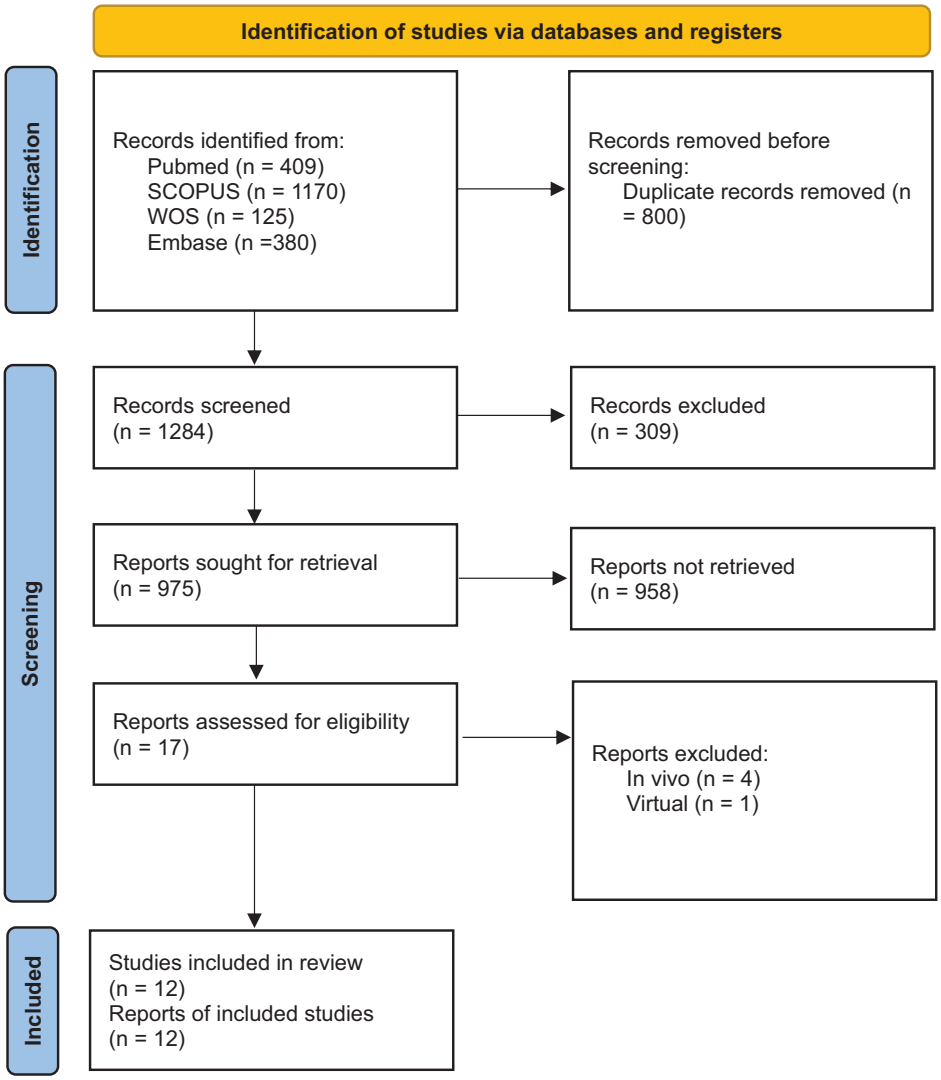

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study.

toxicity profile, treatment Duration (in Months), Object response rate or overall response rate (ORR) (%), PFS OS (mean), complete response rate (CR), partial response rate (PR), stable disease (SD) rate, and progressive disease rate (PD).

2.7 | Data synthesis and meta-analysis

The proper effect size was selected according to the Cochrane Handbook.[14]. We pooled the outcome of radiological response, including CR, PR, SD, and PD, and survival outcomes at different time points using the random effect model by the REML method. The diversity among studies was quantified, and a high level of heterogeneity was deemed to exist if the Q test p-value was < 0.05 and I^2 exceeded 40%. Given the limited number of studies included, we have taken a cautious approach to interpreting our results. Additionally, we sought to offer supplementary insights by considering the 95% confidence interval (CI). It is important to note that using a random effect model links with an overall 95% CI, that is, more CI than fixed effect models, and this aspect should be considered when interpreting these results. STATA V.17 has been used for all statistical analyses.

3 | RESULTS

3.1 | Study characteristics

There were 2084 articles recorded from all recruited databases. Seventeen studies were included for full-text evaluation after being excluded. After removing five research (four in vivo and one virtual), this evaluation looked at 12 studies from 2018 to 2023. Two cohort studies and 10 clinical trials were included in the review. A total of 998 patients, representing case and control groups, were included in the research. GBM was the subject of most investigations; its mean age ranged from 40.2 to 56 years. However, six articles also discuss different gliomas (Figure 1).

TABLE 1 Demographic characteristics.

Author/ Year	Country	Type of study	Number of patients	Gender	Age	Follow up	Number of cases	Number of controls	Type of tumor	Grade of Tumor	Trial phase
Yu 2004	USA	Cohort	40	F (4) M (10)	45	61	14	26	Three (AA), nine (GBM), one (AA-N), and one (GBM-N)	Karnofsky scoring > 60	–
Yao 2017	Germany	Clinical trial	43	F (19) M (24)	48	23	22	21	GBM	Karnofsky scoring > 60	phase II
Yamanaka 2005	Japan	Clinical trial	24	F (8) M (16)	48.9	48.8	24	–	GBM, anaplastic astrocytoma, and glioma	Six grade III & 18 grade IV patients	Phase I/II
Wheeler 2004	USA	Cohort	38	F (19) M (19)	55	33	25	–	GBM	–	–
Prins 2011	USA	Clinical trial	15 (nGBM) 23 (GBM)	F (7) M (16)	51	48	15(nGBM) 23 (GBM)	–	nGBM and rGBM	Grade IV	Phase I
Liau 2023	Canada, Germany, UK	Clinical trial	232 (nGBM) 64 (rGBM)	F (129) M (202)	56	96	232	99	nGBM and rGBM	–	Phase III
Liau 2018	Canada, Germany, UK	Clinical trial	331	F (129) M (202)	56	96	232	99	GBM	–	Phase III
Jie 2012	China	Clinical trial	25	F (3) M (10)	40.2	5.5–24	13	12	GBM	Grade IV	PhaseIII
HU 2021	USA	Clinical trial	36	F (14) M (22)	55.9 (nGBM) 52.3 (rGBM)	48	11 (nGBM) 25 (rGBM)	–	nGBM and rGBM	Grade IV	phase I
Cho 2011	China	Clinical trial	34	F (10) M (8)	55	56	18	16	GBM	Grade IV	–
Chang 2011	China	Clinical trial	17	F (9) M (8)	44.7	48	16	–	GBM	Sixteen grade IV & one grade III	phase I/II

Abbreviations: F, female; M, male; nGBM, newly diagnosed glioblastoma; rGBM, recurrent glioblastoma.

3.2 | DC vaccine administration regimens

Many studies utilized an initial series of vaccinations at short intervals, followed by booster doses at longer intervals. For instance, some trials tested vaccines at intervals of 2 weeks or weekly for the first 3–4 doses.[15,16] Others described more intensive initial regimens of 10 vaccines over 6 months or weekly doses for 10 weeks.[17,18] After the initial serial vaccinations, booster doses were often administered at 2–4-month intervals, with some continuing boosters until vaccine supply exhaustion or disease progression.[8,19–21] The total number of vaccinations ranged widely from just three doses to over 30 doses in some trials[8,21,22] (Table 1).

3.3 | Follow-up duration

The follow-up period was substantially diverse across trials. In the cohort studies, the mean follow-up was 61 and 33 months.[15,22] For clinical trials, follow-up ranged widely from 5.5 months to 8 years.[8,10,16–21,23] Notably, one study did not provide the median or mean follow-up time[24] (Table 1).

3.4 | Outcome metrics of efficacy and safety

The effectiveness outcomes evaluated included median OS (MOS), CR, PR, SD, PD, and PFS at 6, 12, 18, and 24 months, and OS rate. These results give information on the level of anti-tumor activity, ranging from tumor shrinkage to stability to progression events (Table 2).

3.5 | Radiological outcome

3.5.1 | Complete response rate

The incidence of CR was found to be 31% in the study by Jie et al. and 0% in the study by Yamanaka et al.[16,19] A pooled CR of 13% [95%CI: 17%–42%] was calculated, with a Chi-square p-value of 0.02 and an I^2

TABLE 2 Outcomes.

Author/Year	Median overall survival in month	median progression-free survival (median PFS)	6-months PFS	12-months PFS	18-months PFS	24-months PFS	6-months OS	12-months OS	24-months OS	36-months OS	48-months OS	60-months OS
Yu 2004	33.25 (Vaccine) 8.25 (control)	–	–	–	–	–	1	0.785	0.4285	0.357	0.2857	0.071
Yao 2017	13.7 (Vaccine) 10.7 (control)	7.7 (Vaccine) 6.9 (control)	0.545	0.083	0	0	1	0.4545	–	–	–	–
Yamanaka 2005	16 (Vaccine) 13.3 (control)	–	–	–	–	–	0.953	0.6666	0.208	0.125	0.083	–
Wheeler 2004	17.9 (Vaccine) 15.9 (Chemotherapy) 26 (Vaccine & chemotherapy)	–	–	–	–	–	1	0.93	0.083	0	–	–
Prins 2011	35.9 (nGBM) 31.4 (GBM)	15.9	–	–	–	–	–	0.93 (nGBM) 0.91 (GBM)	0.77 (nGBM) 0.55 (GBM)	0.58 (nGBM) 0.47 (GBM)	0.217 (GBM)	0.1304 (GBM)
Liau 2023	19.3 (nGBM) 30.2 (nGBM with methylated MGMT) 13.2 (rGBM)	6.2	–	–	–	–	–	0.76 (nGBM) 0.53 (rGBM)	0.35 (nGBM) 0.203 (rGBM)	0.19 (nGBM) 0.093 (rGBM)	0.15 (nGBM) 0.078 (rGBM)	0.1 (nGBM) 0.031 (rGBM)
Liau 2018	23.1	–	–	–	–	–	–	0.893	0.462	0.254	–	–
Jie 2012	17	–	–	–	–	–	–	0.692	0.077	–	–	–
HU 2021	20.36 (nGBM) 11.97 (rGBM)	8.75 (nGBM) 3.23 (rGBM)	0.723 (nGBM) 0.24 (rGBM)	0.35 (nGBM) 0.15 (rGBM)	–	–	1 (nGBM) 0.92 (rGBM)	0.69 (nGBM) 0.42 (rGBM)	0.2 (nGBM) 0.15 (rGBM)	–	–	–
Cho 2011	31.9 (Vaccine) 15 (control)	8.5	–	–	–	–	1	0.889	0.444	0.167	0.111	0.111
Chang 2011	17.7 (GradeIV GBM) 12.7 (nGBM) 36.2 (rGBM)	–	–	–	–	–	–	–	–	0.32	–	0.188 (GBM) 0.25 (rGBM) 0.125 (nGBM)
Buchroithner 2018	18.9 (overall) 26.6 (methylated MGMT) 11.3 (unmethylated MGMT)	6.9	–	0.284	–	–	–	–	–	–	–	–

Abbreviations: nGBM, newly diagnosed glioblastoma; rGBM, recurrent glioblastoma.

of 82.64%. These results indicate significant heterogeneity across the studies (Figure S1A).

3.6 | Partial response rate

PR was only reported in Jie et al. at 38% and Yamanaka et al. at 21%.[16,19] Pooled PR was 26% [95%CI: 10%–42%], with a Chi-square P-value of 0.27 and an I^2 of 19.10%, indicating low heterogeneity. (Figure S1B).

3.7 | Progressive disease rate

The PD was reported in two articles. Yamanaka et al. reported a PD rate of 41.6%,[19] while Jie et al. reported a lower rate of 7.6%.[16] The pooled PD was 24% [95%CI: 9%–57%] with a high heterogeneity ($I^2 = 86.57\%$, Chi-square p-value = 0.01) (Figure S1C).

3.8 | SD rates

SD rates were reported in two articles. Yamanaka et al. stated a rate of 41.6% and Jie et al. reported a rate of 23%.[16,19] The pooled SD was 33% [95%CI: 15%–51%]. Also, a lower heterogeneity than PD ($I^2 = 31.36\%$, Chi-square p-value = 0.23) was seen (Figure S1D).

3.9 | Progression-free survival

The median PFS reported across the articles ranged from 3.23 to 15.9 months. Yao et al. reported a PFS of 7.7 months in the vaccinated group and 6.9 months in the control group.[23] Prins et al. had the longest reported PFS at 15.9 months, while Hu et al. reported the shortest PFS of 3.23 months in patients with recurrent GBM.[10,20] Other PFS figures included 6.2,[21] 8.5,[18] and 6.9 months.[24] Several articles did not provide data on median PFS.

4 | SIX-MONTH PFS

The 6-month PFS was reported in two articles. Yao et al. reported a 6-month PFS of 54.5%.[23] Hu et al. distinguished between newly diagnosed and recurrent GBM, reporting 6-month PFS rates of 72.3% and 24%, respectively.[10] The remaining articles did not provide data on 6-month PFS. The pooled 6-month PFS was 49% [95%CI: 21%–77%], with a significant degree of heterogeneity (p-value < 0.001, $I^2 = 80.98\%$) (Figure S2A).

5 | TWELVE-MONTH PFS

The 12-month PFS was reported in three of the 12 articles, ranging from 8.3% to 35% in newly diagnosed GBM and 15% in recurrent GBM.[10,23,24] The majority of articles did not provide data on 12-month PFS. The highest 12-month PFS rate reported was 35% in patients with newly diagnosed GBM,[10] while the lowest rate was 8.3%.[23] The pooled 12-month PFS was 19% [95%CI:8%–30%], and the heterogeneity was not statistically significant ($I^2 = 50.22\%$, Chi-square p-value = 0.11) (Figure S2B).

6 | EIGHTEEN-MONTH PFS

The 18-month PFS was reported in two of the twelve articles, with rates of 0% and 69.2%.[16,23] The remaining 10 articles did not provide data on 18-month PFS.

6.1 | Median OS

In the vaccinated population, MOSs ranged from 13.7 months, reported by Yao et al., to a maximum of 33.25 months, reported by Yu et al.[15,23] Four other studies reported MOSs of 16, 17.9, 31.9, and 69.0 months.[17,19,22,24] In the control population, MOSs ranged from 8.25 to a maximum of 18.9 months.[15,24] Wheeler et al. reported MOS in chemotherapy-treated patients at 15.9 and in chemotherapy and vaccine-treated patients at 26 months.[22] Buchroithner et al. reported MOS in methylated MGMT patients at 26.6 months and in unmethylated MGMT patients at 11.3 months.[24] In some studies, MOSs ranged from 12.7 to 20.36 months in newly diagnosed GBMs and 11.97 to 36.2 months in recurrent GBMs.[10,18,21] Also, Liau et al. reported the MOS 30.2 months in nGBMs with methylated MGMT.[21]

7 | SIX-MONTH OS

The 6-month OS across studies of GBM patients ranged from 95.3% to 100%. Specifically, some studies reported 100% 6-month OS.[15,17,22,23] Yamanaka et al. found a 95.3% 6-month OS, while Hu et al. reported 100% survival for newly diagnosed GBM patients and 92% survival for recurrent patients.[10,19] The pooled 6-month OS was 100% [95%CI: 100%–100%] and had a low and negligible heterogeneity ($I^2 = 4\%$, Chi-square p-value = 0.76) (Figure S3).

8 | TWELVE-MONTH OS

The 12-month OS varied across the studies, ranging from 0.454 to 0.93.[22,23] Precisely, the 12-month OS was 0.785,[15] 0.454,[23] 0.666,[19] 0.93 for newly diagnosed GBM and 0.91 for GBM patients,[20] 0.76 for newly diagnosed GBM and 0.53 for recurrent GBM patients,[21] 0.893,[8] 0.692,[16] 0.69 for newly diagnosed GBM and 0.42 for recurrent GBM patients,[10] and 0.889.[17]

The highest 12-month OS was seen in patients with newly diagnosed GBM, while lower rates were observed in patients with recurrent GBM. The pooled 12-month OS was 75% [95%CI: 65%–85%] with a high and significant heterogeneity ($I^2 = 89.87\%$, Chi-square p-value < 0.001) (Figure S4A).

Analyzing studies reported two groups of newly diagnosed GBM and recurrent GBM shows that the pooled 12-month OS for newly diagnosed GBM was 81% [95%CI:68%–94%], with a significant degree of heterogeneity (p-value = 0.05, I^2 = 66.72%). Additionally, the pooled 12-month OS for recurrent GBM was 50% [95%CI:40%–60%] and had a negligible heterogeneity (I^2 = 0%, Chi-square p-value:0.35). The pooled 12-month OS was 67% [95%CI:49%–85%] with a high degree of heterogeneity (I^2 = 89.6%, Chi-square p-value < 0.001), and there was a discernible difference between patients with newly diagnosed GBM and recurrent GBM (p-value < 0.001) (Figure S4B).

9 | TWENTY-FOUR-MONTH OS

The 24-month OS varied widely across the studies, ranging from 7.7% to 77% for newly diagnosed GBM.[16,20] The 24-month OS was reported as 42.8%,[15] 20.8%,[19] 8.3%,[22] 55% for GBM,[20] 35% for newly diagnosed GBM and 20.3% for recurrent GBM,[21] 46.2%,[8] 7.7%,[16] 20% for newly diagnosed GBM and 15% for recurrent GBM,[10] and 44.4%.[17] The pooled 24-month OS was 32% [95%CI: 20%–43%]. The I^2 = 90.29% and Chi-square p-value < 0.001 indicates significant heterogeneity (Figure S5A).

The pooled 24-month OS for newly diagnosed GBM was 44% [95%CI: 12%–76%] with a substantial degree of heterogeneity (p-value < 0.001, I^2 = 90.87%) according to an analysis of studies reporting two groups of newly diagnosed GBM and recurrent GBM. Furthermore, the pooled 24-month OS for recurrent GBM was 19% [95%CI:10%–27%] with low heterogeneity (I^2 = 0%, Chi-square p-value = 0.54). The pooled 24-month OS was 33% [95%CI: 12%–54%] with a high degree of heterogeneity (I^2 = 93.06%, Chi-square p-value < 0.001), and there was no significant difference between patients with newly diagnosed GBM and recurrent GBM (p-value = 0.13) (Figure S5B).

10 | THIRTY-SIX-MONTH OS

The 36-month OS rates reported across the articles ranged from 0% to 58% in patients with newly diagnosed GBM.[20,22] To be precise, Yu et al. reported a 36-month OS of 0.357, Yamanaka et al. reported 12.5%, Prins et al. reported 47% for GBM, Liau et al. reported 19% for newly diagnosed GBM and 0.093 for recurrent GBM, and in 2018 reported 25.4%, Cho et al. reported 16.7%, and Chang et al. reported 32%.[8,15,17–21] The pooled 36-month OS was 23% [95%CI: 12%–33%] with a high and significant heterogeneity (I^2 = 95.28%, Chi-square p-value < 0.001) (Figure S6A).

Analyzing studies reported two groups of newly diagnosed GBM and recurrent GBM shows that the pooled 36-month OS for newly diagnosed GBM was 37% [95%CI:2%–75%], with a significant degree of heterogeneity (p-value < 0.001, I^2 = 88.89%). Additionally, the pooled 36-month OS for recurrent GBM was only reported in one study and was 9% [95%CI:2%–16%]. The pooled 12-month OS was 26% [95%CI:0%–53%] with a high degree of heterogeneity (I^2 = 96.5%, Chi-square p-value < 0.001), and there was no discernible difference between patients with newly diagnosed GBM and recurrent GBM (p-value = 0.17) (Figure S6B).

11 | FORTY-EIGHT-MONTH OS

The 48-month OS varied widely across studies of GBM. Reported 48-month OS rates ranged from 7.8% for recurrent GBM[21] to 28.5% overall,[15] with most studies falling intermediarily at 11.1%,[17] 0.15 for newly diagnosed GBM,[21] and 0.217 overall.[20] The pooled 48-month OS was 13% [95%CI: 8%–17%] and had a low and insignificant heterogeneity (I^2 = 23.48%, Chi-square p-value = 0.25) (Figure S7).

12 | SIXTY-MONTH OS

The reported 60-month OS GBM patients show considerable variability across studies. While one study found a 60-month OS of 7.1%, several others did not provide any 60-month OS data.[15] When specified, rates tended to be higher for newly diagnosed versus recurrent GBM, with one study reporting rates of 10.0% and 3.1%, respectively.[21] The highest reported 60-month OS was 25.0% for newly diagnosed GBM patients.[18] The pooled 60-month OS was 9% [95%CI: 4%–13%] with a modest and minor heterogeneity (I^2 = 36.13%, Chi-square p-value = 0.22) (Figure S8A).

By examining studies that included two groups of patients with newly diagnosed GBM and those with recurrent GBM, it was possible to determine that the pooled 60-month OS for newly diagnosed GBM was 10% [95%CI: 6%–14%], with negligible heterogeneity (P-value = 0.33, I^2 = 0%). Furthermore, the pooled 60-month OS for recurrent GBM was 3% [95%CI: 1%–8%] with low heterogeneity (I^2 = 0%, Chi-square p-value = 0.43). The pooled 12-month OS was 33% [95%CI: 12%–54%] with a high degree of heterogeneity (I^2 = 93.06%, Chi-square p-value < 0.001), and there was a significant difference between patients with newly diagnosed GBM and recurrent GBM (p-value = 0.02) (Figure S8B).

12.1 | Toxicity profile

The toxicity profile of the investigated vaccinations varied across the studies. Mild adverse events like headaches, fatigue, fever, flu-like symptoms, injection site reactions, and myalgia were reported in several studies.[10,15,16,24] More severe events like seizures, disruptions in liver function, decrease in lymphocyte counts, intracranial edema, and lymph node infections were less common, and each occurred in only one or two studies.[15,17,18] Over 200 vaccinations were administered across the studies, and approximately 10%–15% of patients exhibited some kind of adverse reaction, though most were not serious.[10] Overall, the investigated vaccinations appeared relatively well-tolerated, as no concerning trends were seen regarding the safety profile.[8,20,22]

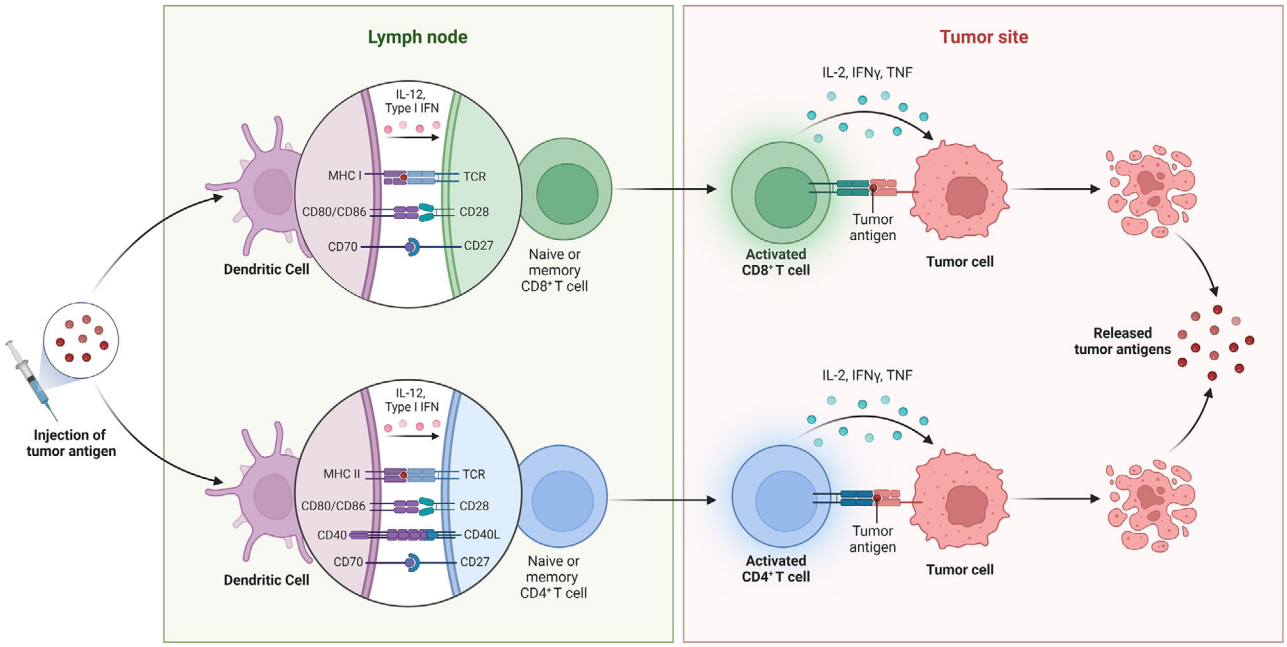

FIGURE 2 Mechanism of action of dendritic cell (DC) vaccine.

12.2 | Publication bias

Regression-based Egger test was recruited to quantify the publication bias. A significant publication bias was noted for 36-month OS ($t = 3.38$, p-value = 0.0096). However, no significant publication bias was noted for 6-Month PFS ($t = 3.20$, p-value = 0.1930), 12-Month PFS ($t = 1.88$, p-value = 0.2015), 6-Month OS ($t = -1.81$, p-value = 0.1297), 12-month OS ($t = -1.84$, p-value = 0.0923), 24-month OS ($t = 1.04$, p-value = 0.3235), 48-month OS ($t = 0.99$, p-value = 0.3797), and 60-month OS ($t = 1.63$, p-value = 0.1546).

Trim-and-fill analysis was also performed to reduce the effect of significant publication bias on the pooled outcome. After adjusting for publication bias, the pooled ORR was 0.393 (95%CI: 0.349–0.437).

12.3 | Sensitivity analysis

The robustness of pooled values was measured by sensitivity analysis, which omitted each study and re-run the meta-analysis to assess the impact of studies on pooled outcomes. A robust outcome was demonstrated for 12-months PFS (p-value < 0.05 for all studies), 6-months OS (p-value < 0.0001 for all studies), 12-months OS (p-value < 0.0001 for all studies), 24-months OS (p-value < 0.0001for all studies), 36-months OS (p-value < 0.0001 for all studies), 48-months OS (p-value < 0.0001 for all studies), 60-months OS (p-value < 0.05 for all studies), PR (p-value < 0.05 for all studies), and SD (P-value < 0.05 for all studies). However, no robust outcome was evident for 6-months PFS (p-value > 0.05 for one study and P-value < 0.05 for another study), CR (p-value > 0.05 for one study and p-value < 0.05 for another study), and PD (p-value > 0.05 for one study and p-value < 0.0001for another study).

13 | DISCUSSION

DCs loaded with GBM antigens are used in DC vaccines to activate T cells generating an immune response against GBM[25,26] (Figure 2). These vaccines are made by removing DCs from the patient's blood, re-injecting the cells to trigger an anti-tumor immune response, and exposing the cells to tumor lysate or peptides to load them with antigens.[27] Major obstacles include developing a strong cytotoxic T-cell response, GBM's immunosuppressive characteristics, and limited DC migration to lymph nodes.[28] According to Hotchkiss et al., there is ongoing research into the DC vaccine, including delivery techniques, toll-like receptor agonists, combinations with checkpoint inhibitors, and antigen-loading optimization.

DC vaccines show promising immunotherapy for GBM, with studies indicating improved efficacy and safety compared to treatments like chemotherapy and radiation.[2,29] Key advantages include generating systemic anti-tumor immunity through activation of T cells,[25,27] capability for personalized medicine approaches,[28] and synergistic combination potential with emerging immunotherapies.[30,31] However, additional randomized controlled trials are still needed to demonstrate the clinical benefits fully and to complete the translation to practice.[28,32]

DC vaccines demonstrate therapeutic potential for newly diagnosed GBM based on early-phase clinical trials showing improved PFS and OS with minimal toxicity.[2,29] Evidence also supports use in recurrent GBM settings, where DC vaccines may overcome tumor immune evasion mechanisms acquired during prior therapy, like chemotherapy and radiation.[25,28]

This systematic review and meta-analysis of 12 studies evaluating DC vaccines for glioma treatment provides insightful data on efficacy and safety. Several key findings emerge regarding survival benefits,

response rates, impact of disease stage, and tolerability. Across the 12 studies examined, several notable trends surround survival outcomes, response rates, and disease control rates.

Overall survival rates showed general favorability with DC vaccination, particularly at earlier times. The pooled 6-month OS reached 100% 95%CI: 100%–100%), and the 12-month OS reached 75% (95%CI: 65%–85%).[19,22] These high early survival rates suggest possible benefits of DC vaccines during the initial treatment stages. However, OS declined substantially afterward, with pooled 24-month OS at only 32% (95%CI: 20%–43%) and 36-month OS at 23% (95%CI: 12%–33%).[15,19] Thus, long-term impacts appear limited. Further, newly diagnosed GBM patients trended toward more favorable OS than recurrent cases.[10,21] This aligns with the greater treatment resistance seen in relapse.[20] Hence, earlier vaccination may confer better outcomes.

PFS metrics showed similar trends of declining efficacy over time. Pooled 6-month PFS reached 49% (95%CI: 21%–77%) but dropped to 19% (95%CI: 8%–30%) by 12 months with high study heterogeneity ($I^2 = 80.98\%$).[23] Comparisons based on disease stage further support preferential benefits with early vaccination.[10] For both PFS and OS, the higher heterogeneity at later time points indicates increasing variability in longer-term prognosis. This may reflect differences in maintenance therapy and individual patient factors.[19] Nonetheless, the overall patterns highlight the challenges of sustaining responses.

In terms of radiographic response, pooled CR remained low at 13% (95%CI: 17%–42%), as did pooled PR at 26% (95%CI: 10%–42%).[16,19] On the other hand, disease stabilization was more common than tumor regression, as indicated by PD reaching 24% (95%CI: 9%–57%) and SD reaching 33% (95%CI: 15%–51%).[16,19] Therefore, cytostatic effects appear to outweigh cytoreductive effects, which is consistent with the observed survival improvements. Even if the base does not match the requirements for an objective response, it might be related to increased anti-tumor immunity.[18]

13.1 | Limitation

Certain limitations should be noted regarding the quality of the evidence. All the DC vaccine trials were in the early phase, with 10 being phase I/II studies. Many had small sample sizes of under 100 patients without control groups.[19,22] This restricts statistical power and comparisons. Additionally, substantial heterogeneity existed across the investigations in factors ranging from glioma subtype to vaccination regimens used. However, the overall concordance in survival and response trends supports meaningful interpretation of the data synthesis.

14 | CONCLUSION

The meta-analysis reveals that DC vaccinations offer benefits in treating gliomas, leading to prolonged early survival and disease control when resistance to treatment is low. However, these benefits diminish significantly over time and are not very stable. While CR is rare, stabilization occurs frequently, highlighting the predominantly cytostatic nature of the treatment. The effectiveness of DC therapy could be enhanced by combining it with other immunotherapies, increasing vaccine potency, and classifying patients based on biomarkers. These strategies will contribute to further harnessing the potential of DC in the evolving landscape of glioma therapy. Integrating DC therapy as a supplementary treatment for newly diagnosed cases is the most effective clinical approach.

AUTHOR CONTRIBUTIONS

Mohammad Amin Habibi, Mohammad Sina Mirjani, and Muhammad Hussain Ahmadvand wrote the manuscript; Pouria Delbari, Shayan Arab, Poriya Minaee, and SeyedMohammad Eazi reviewed and revised the manuscript. Sajjad Ahmadpour is correspondence. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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There is no funding source with authors to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study is deemed exempt from receiving ethical approval.

ORCID

Sajjad Ahmadpour https://orcid.org/0000-0003-4321-874X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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