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ORIGINAL RESEARCH

Efficacy and safety analysis on dendritic cell-based vaccine-treated high-grade glioma patients: a systematic review and meta-analysis

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Background: Dendritic cell (DC)-based vaccine is a promising therapy for high-grade gliomas (HGGs); however, its actual effectiveness still remains controversial. This meta-analysis aims to extensively evaluate the efficacy and safety of DC vaccine for HGG patients.

Methods: We systematically searched PubMed, the Cochrane Library, EMBASE, Medline, and Web of Science for relevant parallel randomized controlled trials (RCTs) and properly controlled non-randomized studies (NRS) published in English. Two investigators reviewed all the texts and extracted information regarding overall survival (OS), progression-free survival (PFS), and adverse events (AEs) from eligible studies. Sensitivity analyses and subgroup analyses were also conducted.

Results: Of 353 suitable studies, 13 studies (three RCTs and ten NRS) involving 944 patients were finally included. Compared to the control therapy group (CT group), the DC group showed better OS and PFS without serious AEs. Subgroup analysis showed that trials designed as NRS obtained better results in the DC group in this study; however, no specific subgroup regarding dosages, cycles or injection routes was found to be superior in the DC group compared to the CT group.

Conclusion: DC vaccine can significantly improve OS and PFS, with acceptable toxicity, of HGG patients. Nevertheless, further studies are needed to verify this conclusion.

Keywords: dendritic cell, vaccine, glioblastoma multiforme, high-grade gliomas, overall survival, progression-free survival

Introduction

High-grade gliomas (HGGs) generally consist of anaplastic astrocytomas (WHO grade III) and glioblastoma multiforme (GBM; WHO grade IV), anaplastic oligodendrogliomas (WHO grade III), and the rare anaplastic oligoastrocytomas (WHO grade III), among which, GBM is the most frequent and common type of HGG in primary malignant brain tumors, with an incidence of 3–4 per 100,000, accounting for 15.6% of all primary brain tumors and 45.2% of primary malignant brain tumors.[1] The current standard treatment for HGG patients includes maximal surgical resection, followed by concurrent high-dose radiation and temozolomide (TMZ) chemotherapy.[2] However, prognosis of GBM patients remains dismal, with a median survival of 15 months[3] and only 25% surviving at 2 years after initial diagnosis.[4] Therefore, new treatment modalities are urgently needed.

Autologous dendritic cell (DC)-based immunotherapy is one of the promising, novel approaches for HGG treatment.[5] DCs are a specialized family of professional antigen presenting cells with the broadest range of antigen presentation and unique ability to initiate and maintain primary immune responses when pulsed with tumor

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associated antigens (TAAs).[6,7] As in vaccine preparation, DCs are extracted from the patient, cultured ex vivo, loaded with TAAs, and subsequently reintroduced into the patient to facilitate antigen-specific T-cell activation.[8]

During the past few decades, DC vaccines have been clinically investigated in a vast range of malignancies, including prostate cancer, renal cell carcinoma, melanoma, and even glioma. Regarding HGGs (malignant glioma), multiple Phase I/II trials have been reported; however, the objective response rate was only 15.6%.[9] Conversely, two meta-analysis published in 2014 indicated improved overall survival (OS) and progression free-survival (PFS) were obtained through DC vaccination in HGG patients.[10,11] With more clinical trials completed in the past few years, we are trying to synthesize the data for the efficacy and safety of DC vaccine application in HGG patients with freshly updated retrievals from both randomized clinical trials (RCTs) and properly controlled non-randomized controlled studies (NRS).

Methods

Since this study is a meta-analysis of previously published studies, ethical approval and patient consent were not required.

This study was conducted and reported in adherence to Preferred Reporting Items for Systematic Reviews and Meta-analysis.[12] The PRISMA checklist was reported in Figure S1.

Literature search strategy

A systematic search of several online databases (PubMed, EMBASE, ISI Web of Science and Cochrane Library) was performed for original articles published in English language up to June 15, 2018 relevant to DC vaccine for HGGs. Clinical trials registered on the website ClinicalTrials.gov were also explored. The following search terms were applied to identify relevant studies: "High-grade gliomas" or HGGs or glioblastoma or GBM or "anaplastic astrocytomas" OR "anaplastic oligodendrogliomas" OR "anaplastic oligoastrocytomas", and "dendritic cell" or DC. Results from these databases were imported into the software of Endnote X7.7 for duplication checking to obtain a list of unique articles for subsequent screening. Gray literature was not included in the present analysis.

For Medline, we used the following search strategies, Search ((((((((((glioma OR "Anaplastic Astrocytoma" OR "Glioblastoma Multiforme" OR "High-grade glioma" OR astrocytomas OR oligodendrogliomas)) AND dendritic)) NOT ((mice OR animal OR rats OR murine)))) AND English[Language])) NOT (("in vitro" [Title/Abstract]) OR "cell line" [Title/Abstract]))) NOT ((review [Publication Type]) OR review).

Selection criteria

The following criteria were applied when considering studies for this meta-analysis.

Types of studies

The meta-analysis considered studies evaluating the effectiveness or efficacy of DC vaccine for patients with HGGs. The studies must have compared the intervention with no intervention or with a control intervention. RCTs or properly controlled NRS were eligible for inclusion.

Types of participants

Patients with primary or recurrent HGGs were included.

Types of interventions

Patients in the treatment group must have received DC vaccination. Patients in the control group must have been treated with conventional therapy without DC vaccine.

Types of outcome measures

Results must have included quantitative data for outcomes measured. The primary outcomes were OS and PFS. The secondary outcome was treatment-related adverse events (AEs), which included treatment-related withdrawals and discontinuations.

Conference abstracts and other forms of summary publication were excluded. In the case of multiple studies apparently based on the same population, only the study with the largest number of participants was included.

Data collection

References were managed using EndNote X7.7 software (Thomson Reuters, New York, NY, USA). Two authors (CLL, TL) independently screened studies identified in literature searches. Discrepancies were arbitrated by two other authors (BZ, YZ). Two authors (CLL, TL) independently extracted data from included studies using a predefined template. BZ and YZ checked the extracted data against the original studies.

Survival data and AEs were taken directly from tables or the text whenever possible; if such data were presented only in Kaplan–Meier curves, they were read by the Engauge Digitizer version 10.4 (free software downloaded from http://sourceforge.net).

Assessment of methodological quality of included studies

For the RCTs and NRS, Cochrane bias assessment tool and Newcastle-Ottawa scale[13] (NOS) were applied, respectively. Two authors (CLL and TL) independently assessed methodological quality of included studies, Discrepancies were arbitrated by HYY and YS.

Data synthesis and analysis

Statistical analysis was mainly performed using STATA SE (StataCorp LP, College Station, TX, USA). Pooled RRs using the Mantel–Haenszel method were calculated for dichotomous data. The homogeneity of the effect size across studies was tested using Q statistics, I^2 statistic was also used to assess statistical heterogeneity in the meta-analysis (high heterogeneity >50%; low heterogeneity, <50%). Data were analyzed using fixed-effects models when $P>0.10$ for the Q statistic; otherwise random-effects models were used.[14] For the meta-analysis of each outcome, we conducted pre-planned sensitivity analyses restricted to trials that included the efficacy of DC. Publication bias was assessed using Begg's funnel plots test[15] and Egger's regression test,[16] when studies included were more than ten.[17] P-value <0.05 was considered to be significant, except where otherwise specified.

Results

Study selection

A total of 353 potentially eligible studies were identified and reviewed. According to inclusion criteria, 241 studies remained after removing the duplicates. Screening of the titles and abstracts led to a final set of 42 studies that were read in full. Of these, 25 studies were excluded because they were not appropriately controlled, and four other studies were excluded due to absence of data for analysis. Eventually, three RCTs[18–20] and ten NRS, including five non-randomized controlled trials,[21–25] four historically controlled studies,[26–29] and one cohort study,[30] involving 307 DC-vaccinated (DC group) and 637 non-DC-vaccinated (CT group: control therapy group) patients, were included in the meta-analysis. The detailed selection process was described in Figure 1, according to the PRISMA Statement for reviews and meta-analysis.[31]

Studies' characteristics

The characteristics of the 13 included studies were described in Table 1, and the outcome data for OS and PFS were presented in Table 2.

Five studies were from America, four from Europe, and the rest from Asia. All studies enrolled patients with HGGs of grade III anaplastic astrocytomas (AA), and/or IV (GBM). One cohort study,[30] two pilot studies,[21,26] four Phase I trials,[22,25,27,29] three Phase II trials,[18–20] and three Phase I/II trials were included in these studies.[23,24,28] Most of the studies enrolled patients with Karnofsky performance scale (KPS) score of ≥60,[20,22,23,25,27] two studies with KPS score of ≥70,[19,28] and only one study with KPS score of ≥80.[29] However, there were still five studies without inclusion criteria for KPS score or relative data not available.[18,21,24,26,30] All studies contained at least two arms, one arm was conventional treatment, such as surgery, radiation, and TMZ chemotherapy, while the other arm had the addition of DC vaccination. For 7/13 studies, surgery, radiation, and chemotherapy were applied in both arms.[18–20,22,24,26,27,29] Surgery and radiation were applied in two studies.[21,28] In a non-RCT study, only chemotherapy was used as the control arm,[23] while in the cohort study, re-radiation therapy (always concomitant with re-operation) was used as the control arm and re-operation plus DC vaccine was used as the treatment arm.[30]

The activation of DCs was achieved in different ways in different studies. Although autologous tumor lysates (ATL) were commonly used to activate DCs in these studies,[18–21,24,25,27] HLA-1-eluted peptides,[23] and acid eluted MHC-I enriched peptides were also alternatives to pulsed DCs.[22] Autologous glioblastoma stem cell mRNA[26] and cytomegalovirus pp65 mRNA[29] transfected DCs were administered in two other studies.

The dosage of DCs injected ranged from 10^6–10^8, and the vaccination cycles also varied greatly in different studies. The injection routes of DC administration mainly included intradermal (ID),[22,24–27,29] intratumoral (IT),[24] subcutaneous (SC),[19–21,28] and inguinal lymph node injection.[18]

OS

OS was assessed at the time point of 0.5 year, 1 year, 2 years, 3 years, 4 years, and 5 years, as shown in Table 3 (forest plots were included in Figure S2). No heterogeneity was observed, and fixed-effects models were used. We found that in all of the time points specified, OS was significantly better in DC group than that in CT group, except at the time point of half a year (P=0.391, pooled RR =1.058, 95% CI =0.930–1.203).

PFS

PFS analysis was performed at the time point of 0.5 year, 1 year, 2 years, 3 years, and 4 years (data were shown in Table 4

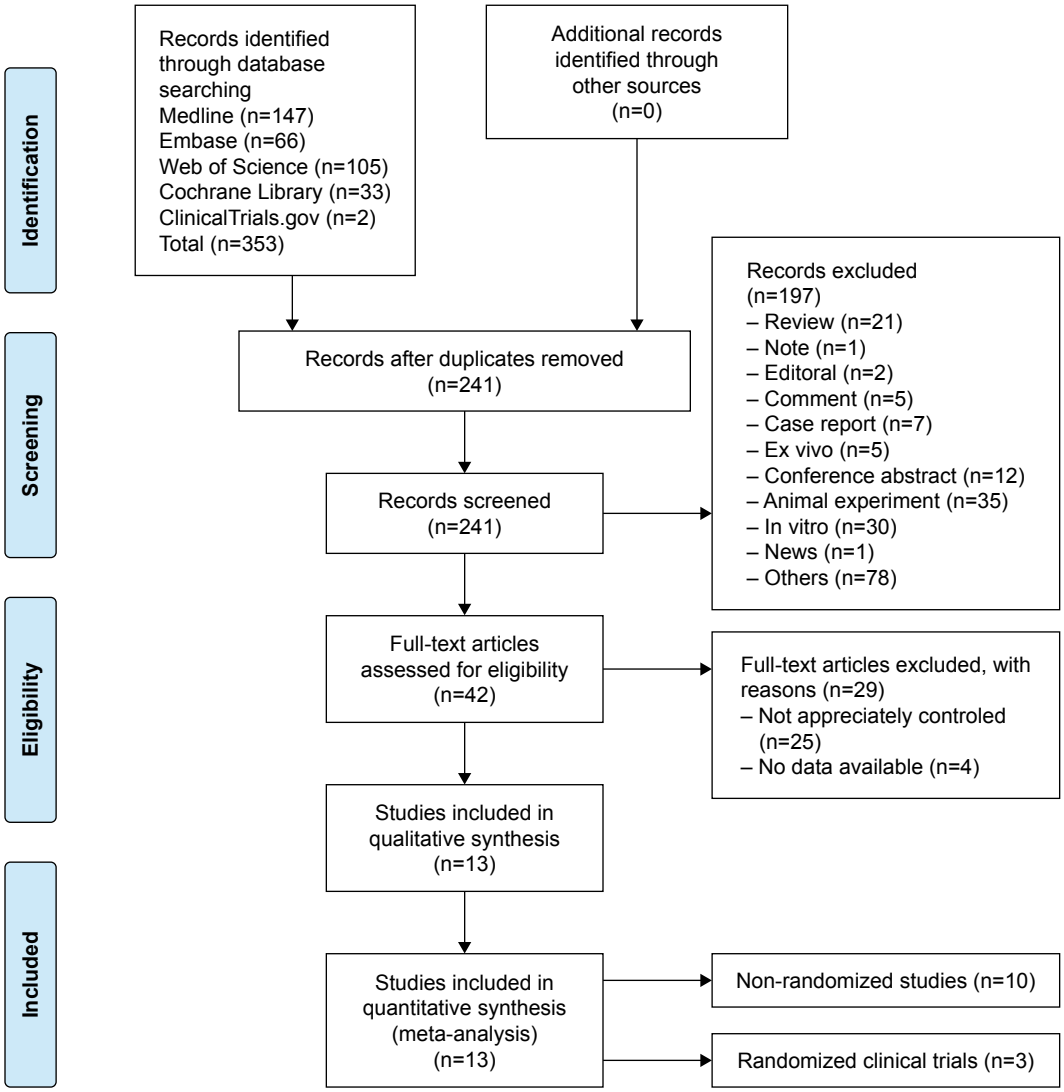

Figure 1 Study selection process.

and forest plots were included in Figure S3). No advantages were observed in DC group in both 0.5-year PFS and 1-year PFS, although different models were used. In contrast, significantly better PFS data were found in DC group compared with CT group from the time point of 2 years (P=0.000, pooled RR =8.592, 95% CI =2.944–25.077), 3 years (P=0.006, pooled RR =9.302, 95% CI =1.924–44.969), and 4 years (P=0.039, pooled RR =8.017, 95% CI =1.109–57.950).

Subgroup analysis

Subgroup analysis was conducted according to regions (America vs Asia vs Europe), study design (NRS vs RCTs), method of DC activation (peptides vs ATL vs DNA constructs vs fusion of tumor cell lines), dosages ($<2\times10^7$ vs $\geq2\times10^7$), cycles (<4 vs ≥4), and route of injections (ID vs SC). Results were only reported for 1-year OS, 2-year OS, and 3-year OS, as shown in Table 5. Studies published in America showed significant enhancement with DC vaccination in both 2-year OS ($P<0.001$, pooled RR =2.488, 95% CI =1.656–3.738) and 3-year OS ($P<0.001$, pooled RR =4.574, 95% CI =2.312–9.048); however, studies published in Asia also obtained better results in DC group in 3-year OS analysis (P=0.001, pooled RR =12.141, 95% CI =2.603–56.616). NRS indicated significant enhancement in DC group in both 1-year OS (P=0.018, pooled RR =1.226, 95% CI =1.036–1.450), 2-year OS ($P<0.001$, pooled RR =1.806, 95% CI =1.361–2.395), and 3-year OS (P=0.001, pooled RR =2.678, 95% CI =1.730–4.145). Different types of activation of DCs showed significant difference between DC group and CT group in 2-year OS, except for peptides' activation (P=0.080, pooled RR =1.983, 95% CI =0.922–4.266), perhaps due to the limited study numbers

Table 1 Characteristics of the studies included

Study	Nation	Study design disease stage (WHO)		Clinical trial phase	Pts no (DC/total)	Median/ mean age (DC/CT)	Inclusion KPS score	Control arm	DC arm	DC characteristics			
										Activation	Dosage (106)	Cycles	Route
Yu et al,[25] 2004	USA	NRS[a]	III–IV	I	14/40	46/53	≥60	S+R	S+R+DC	ATL	10–100	3	ID
Wheeler et al,[23] 2004	USA	NRS[a]	III–IV	I/II	13/26	54/56	>60	C	C+DC	HEP/ATL	10–40	3	N/A
Yamanaka et al,[24] 2005	Japan	NRS[a]	III–IV	I/II	18/45	50/56	N/A	S+R+C	S+R+C+DC	ATL (KLH/P. pyogenes)	1–32	2–22	ID/IT
Liau et al,[22] 2005	USA	NRS[a]	IV	I	12/111	42/N/A	≥60	S+R/(+C)	S+R/(+C)+ DC	AMP	1–10	12	ID
Leplina et al,[21] 2007	RU	NRS[a]	III–IV	Pilot	39/119	43/46	N/A	S+R	S+R+DC	ATL (Roncoleukin)	10	6	SC
Chang et al,[28] 2011	China	NRS[b]	III–IV	I/II	17/80	45/N/A	≥70	S+R	S+R+DC	Fusion	10–60	10	SC
Prins et al,[27] 2011	USA	NRS[b]	IV	I	9/91	53/N/A	≥60	S+R+C	S+R+C+DC	ATL	1–10	~10	ID
Cho et al,[19] 2012	China	RCT	IV	II	18/34	52/56	>70	S+R+C	S+R+C+DC	Fusion	20–50	10	SC
Jie et al,[20] 2012	China	RCT	IV	II	13/25	40/43	≥60	S+R+C	S+R+C+DC	ATL (heat-shocked)	1	4	SC
Buchroithner et al,[18] 2014	Austria	RCT	IV	II	19/40	N/A	N/A	S+R+C	S+R+C+DC	ATL (LPS/IFN-γ)	N/A	10	IN
Vik-Mo et al,[26] 2013	Norway	NRS[b]	IV	Pilot	7/17	57/62	NA	S+R+C	S+R+C+DC	GSC-mRNA	10	12	ID
Müller et al,[30] 2015	Germany	NRS[c]	III–IV	N/A	117/282	N/A	N/A	ReRT/ReOP	ReOP+DC	N/A	N/A	N/A	N/A
Batich et al,[29] 2017	USA	NRS[b]	IV	I	11/34	55/NA	≥80	S+R+C	S+R+C+DC	pp65-mRNA	20	3	ID

Notes: NRS,[a] non-randomized controlled trial; NRS,[b] cohort study; NRS,[c] historically controlled study. Fusion, fusion of DC and tumor cells; GSC-mRNA, autologous glioblastoma stem cell mRNA transfected; pp65-mRNA, cytomegalovirus pp65 mRNA transfected.

Abbreviations: RU, Russian Federation; RCT, randomized controlled trial; NRS, non-randomized controlled study; Pts, patients; DC, dendritic cell; CT, control therapy; KPS, Karnofsky performance score; S, surgery; R, radiation; C, chemotherapy; ReRT, re-radiation; ReOP, reoperation; ATL, autologous tumor lysates; HEP, HLA-1-eluted peptide; KLH, keyhole limpet hemocyanin; P. pyogenes, penicillin-killed *Streptococcus pyogenes*; AMP, acid eluted MHC-I enriched peptides; ID, intradermal; IT, intratumoral; SC, subcutaneous; IN, inguinal lymph node injection; N/A, no data.

Table 2 Original data extracted from included studies

Study	Year	Sample size (DC/control)	0.5-year OS (Pts, %)	1-year OS (Pts, %)	2-year OS (Pts, %)	3-year OS (Pts, %)	4-year OS (Pts, %)	5-year OS (Pts, %)	0.5-year PFS (Pts, %)	1-year PFS (Pts, %)	2-year PFS (Pts, %)	3-year PFS (Pts, %)	4-year PFS (Pts, %)
Wheeler et al[23]	2004	13	13, 100%	12, 92.3%	7, 53.8%	2, 15.4%	1, 7.7%	/	/	/	/	/	/
		13	13, 100%	8, 61.5%	2, 15.4%	0	0	/	/	/	/	/	/
Yu et al[25]	2004	14	14, 100%	11, 78.6%	6, 42.9%	5, 35.7%	4, 28.6%	1, 7.1%	/	/	/	/	/
		26	15, 57.7%	7, 26.9%	2, 7.7%	2, 7.7%	0	0	/	/	/	/	/
Liau et al[22]	2005	12	12, 100%	9, 75.0%	6, 50.0%	3, 25.0%	2, 16.7%	2, 16.7%	10, 83.3%	9, 75.0%	5, 41.7%	2, 16.7%	/
		99	97, 98.0%	60, 60.6%	20, 20.2%	5, 5.1%	2, 2.0%	1, 1.0%	68, 68.7%	32, 32.3%	4, 4.0%	1, 1.0%	/
Yamanaka et al[24]	2005	18	16, 88.9%	11, 61.1%	4, 22.2%	2, 11.1%	1, 5.6%	/	/	/	/	/	/
		27	24, 88.9%	16, 59.3%	1, 3.7%	0	0	/	/	/	/	/	/
Leplina et al[21]	2007	39	/	29, 74.4%	14, 35.9%	4, 10.3%	/	/	/	/	/	/	/
		80	/	42, 52.5%	22, 27.5%	15, 18.8%	/	/	/	/	/	/	/
Chang et al[28]	2011	17	16, 15.1%	11, 64.7%	7, 41.2%	6, 35.3%	4, 23.6%	3, 23.1%	/	/	/	/	/
		63	51, 81.0%	35, 55.6%	7, 11.1%	0	0	0	/	/	/	/	/
Prins et al[27]	2011	9	9, 100%	8, 88.9%	5, 55.6%	5, 55.6%	4, 44.4%	4, 44.4%	/	/	/	/	/
		82	82, 100%	58, 70.7%	20, 24.4%	10, 12.2%	8, 9.8%	5, 6.1%	/	/	/	/	/
Cho et al[19]	2012	18	18, 100%	16, 88.9%	8, 44.4%	3, 16.7%	2, 11.1%	/	12, 66.7%	7, 38.9%	3, 16.7%	2, 11.1%	2, 11.1%
		16	16, 100%	12, 75.0%	4, 25.0%	0	0	/	13, 81.3%	13, 81.3%	0	0	0
Jie et al[20]	2012	13	12, 92.3%	9, 69.2%	1, 7.7%	/	/	/	12, 92.3%	/	/	/	/
		12	12, 100%	5, 41.7%	0	/	/	/	11, 91.7%	/	/	/	/
Vik-Mo et al[26]	2013	7	7, 100%	6, 85.7%	5, 71.4%	/	/	/	7, 100%	6, 85.7%	3, 42.9%		
		10	10, 100%	8, 80.0%	3, 30.0%	/	/	/	8, 80.0%	1, 10.0%	0		
Buchroithner et al[18]	2014	19	/	17, 89.5%	/	/	/	/	/	/	/	/	/
		21	/	13, 61.9%	/	/	/	/	/	/	/	/	/
Müller et al[30]	2015	117	84, 71.8%	41, 35.0%	15, 12.8%	7, 6.0%	5, 4.3%	1, 0.9%	/	/	/	/	/
		165	103, 62.4%	44, 26.7%	17, 10.3%	5, 3.0%	4, 2.4%	3, 1.8%	/	/	/	/	/
Batich et al[29]	2017	11	11, 100%	11, 100%	8, 72.7%	6, 54.5%	4, 36.4%	4, 36.4%	11, 100%	8, 72.7%	6, 54.5%	4, 36.4%	4, 36.4%
		23	22, 95.7%	12, 52.2%	4, 17.4%	0	0	0	18, 78.3%	5, 21.7%	0	0	0

Abbreviations: DC, dendritic cell; OS, overall survival; Pts, patients; PFS, progression-free survival.

Table 3 OS analysis at the time point of 0.5 year, 1 year, 2 years, 3 years, 4 years, and 5 years

Subgroups	No of studies	No of patients		Heterogeneity		Model	M–H pooled RR	95% CI		Z value	*P* sig
		DC group	CT group	*P*-value	I^2 (%)			Lower	Upper		
0.5-year OS	11	249	536	0.999	0.0	Fixed	1.058	0.930	1.203	0.86	0.391
1-year OS	13	307	637	0.995	0.0	Fixed	1.222	1.050	1.423	2.58	0.010
2-year OS	12	288	616	0.764	0.0	Fixed	1.792	1.366	2.353	4.21	0.000
3-year OS	13	268	594	0.097	39.2	Fixed	2.750	1.783	4.242	4.58	0.000
4-year OS	9	229	508	0.722	0.0	Fixed	4.532	2.427	8.461	4.74	0.000
5-year OS	6	180	458	0.266	22.3	Fixed	4.801	2.280	10.108	4.13	0.000

Abbreviations: OS, overall survival; DC, dendritic cell; CT, control therapy; M–H, Mantel–Haenszel; sig, significance.

Table 4 PFS analysis at the time points of 0.5 year, 1 year, 2 years, 3 years, and 4 years

Subgroups	No of studies	No of patients		Heterogeneity		Model	M–H pooled RR	95% CI		Z value	*P* sig
		DC group	CT group	*P*-value	I^2 (%)			Lower	Upper		
0.5-year PFS	5	61	160	0.975	0.0	Fixed	1.051	0.812	1.360	0.38	0.740
1-year PFS	4	48	148	0.049	61.9	Random	1.551	0.745	3.229	1.17	0.241
2-year PFS	4	48	148	0.940	0.0	Fixed	8.592	2.944	25.077	3.94	0.000
3-year PFS	3	41	138	0.780	0.0	Fixed	9.302	1.924	44.969	2.77	0.006
4-year PFS	2	29	39	0.565	0.0	Fixed	8.017	1.109	57.950	2.06	0.039

Abbreviations: PFS, progression-free survival; DC, dendritic cell; CT, control therapy; M–H, Mantel–Haenszel; sig, significance.

Table 5 The outcome of subgroup analysis of DC vs CT regarding 1-year, 2-year, and 3-year OS

Subgroups	No of studies	Pooled RR	95% CI		*P* sig	No of studies	Pooled RR	95% CI		*P* sig	No of studies	Pooled RR	95% CI		*P* sig
			Lower	Upper				Lower	Upper				Lower	Upper	
Regions															
Total	13	1.222	1.050	1.423	0.010	12	1.792	1.366	2.353	0.000	10	2.750	1.783	4.242	0.000
America	5	1.275	0.999	1.626	0.051	5	2.488	1.656	3.738	0.000	5	4.574	2.312	9.048	0.000
Asia	4	1.118	0.770	1.624	0.557	4	2.161	0.892	5.231	0.088	3	12.141	2.603	56.616	0.001
Europe	4	1.229	0.971	1.533	0.087	3	1.273	0.844	1.919	0.249	2	1.003	0.482	2.087	0.994
Study designs															
Total	13	1.222	1.050	1.423	0.010	12	1.792	1.366	2.353	0.000	10	2.750	1.783	4.242	0.000
NRS	10	1.226	1.036	1.450	0.018	10	1.806	1.361	2.395	0.000	9	2.678	1.730	4.145	0.000
RCT	3	1.206	0.843	1.727	0.306	2	1.651	0.610	4.460	0.324	1	5.409	0.299	97.796	0.253
DC activation															
Total	11	1.222	0.050	1.423	0.010	10	1.792	1.366	2.353	0.000	8	2.750	1.783	4.242	0.000
ATL	6	1.260	1.006	1.579	0.044	5	1.747	1.133	2.693	0.012	4	1.639	0.917	2.927	0.095
Peptides	1	1.136	0.667	1.935	0.640	1	1.983	0.922	4.266	0.080	1	4.160	1.106	15.651	0.035
Fusion	2	1.099	0.748	1.615	0.630	2	2.147	1.074	4.292	0.031	2	14.944	2.388	93.511	0.004
mRNA	2	1.282	0.790	2.081	0.315	2	2.359	1.077	5.168	0.032	1	17.333	1.043	288.127	0.047
Dosages															
Total	7	1.222	1.050	1.423	0.010	7	1.792	1.366	2.353	0.000	5	2.750	1.783	4.242	0.000
$<2\times10^7$	5	1.192	0.936	1.518	0.154	5	1.550	1.060	2.266	0.024	3	1.466	0.821	2.620	0.196
$\geq2\times10^7$	2	1.247	0.825	1.885	0.296	2	2.089	1.004	4.345	0.049	2	10.557	1.501	74.237	0.018
Cycles															
Total	10	1.222	1.050	1.423	0.010	9	1.792	1.366	2.353	0.000	7	2.750	1.783	4.242	0.000
<6	4	1.513	1.052	2.175	0.025	4	3.052	1.492	6.245	0.002	3	6.095	1.831	20.288	0.003
≥6	6	1.165	0.944	1.438	0.155	5	1.644	1.141	2.370	0.008	4	2.032	1.092	3.782	0.025
Routes															
Total	9	1.222	1.050	1.423	0.010	9	1.792	1.366	2.353	0.000	7	2.750	1.783	4.242	0.000
ID	5	1.300	0.983	1.720	0.066	5	2.275	1.467	3.530	0.000	4	4.592	2.290	9.205	0.000
SC	4	1.190	0.922	1.536	0.182	4	1.571	1.014	2.434	0.043	3	1.769	0.874	3.579	0.113

Abbreviations: DC, dendritic cell; CT, control therapy; OS, overall survival; sig, significance; NRS, non-randomized controlled study; RCT, randomized controlled trial; ATL, autologous tumor lysates; ID, intradermal; SC, subcutaneous.

(only one) in this group. No specific dosages, cycles or injection routes were found to be superior in the subgroup analysis, since significant difference between DC group and CT group regarding 2-year OS was found in all the groups within these subgroups.

AEs

The most frequent AEs were low-grade fever, fatigue, and myalgia.[20,22,25–27] Injection site reactions, including erythema, pain, and itching, were reported in four studies.[22,24,25,27] Nausea, vomiting, constipation, and diarrhea were recorded in three studies.[22,26,27] Severe vaccine-related AEs were only reported in two studies. Chang et al reported Grade III (3/17) and Grade IV (2/17) lymphopenia in DC group,[28] while Batich et al noted only one Grade III AE attributable to GM-CSF administration.[29] No death related to DC vaccination was reported in the included studies.

Risk of bias

Three RCT studies were assessed by Cochrane risk of bias tool with Revman 5.3. As shown in Figure 2, most of the judgements for the three RCT studies were low risk of bias or unclear, with only one high risk of bias reported for Buchroithner et al. In that trial, data were not completely documented.[18]

NRS was assessed by NOS[13] as shown in Table 6, most of the studies scored more than six stars, indicating low risk of bias, with only one cohort study scoring five stars.[30]

Sensitivity analysis

Sensitivity analysis was performed to explore an individual study's influence on the pooled results by deleting one single study each time from pooled analysis. Regarding 0.5-year OS, 1-year OS, 2-year OS, 3-year OS, 4-year OS, and 5-year OS, the results showed that no substantial change

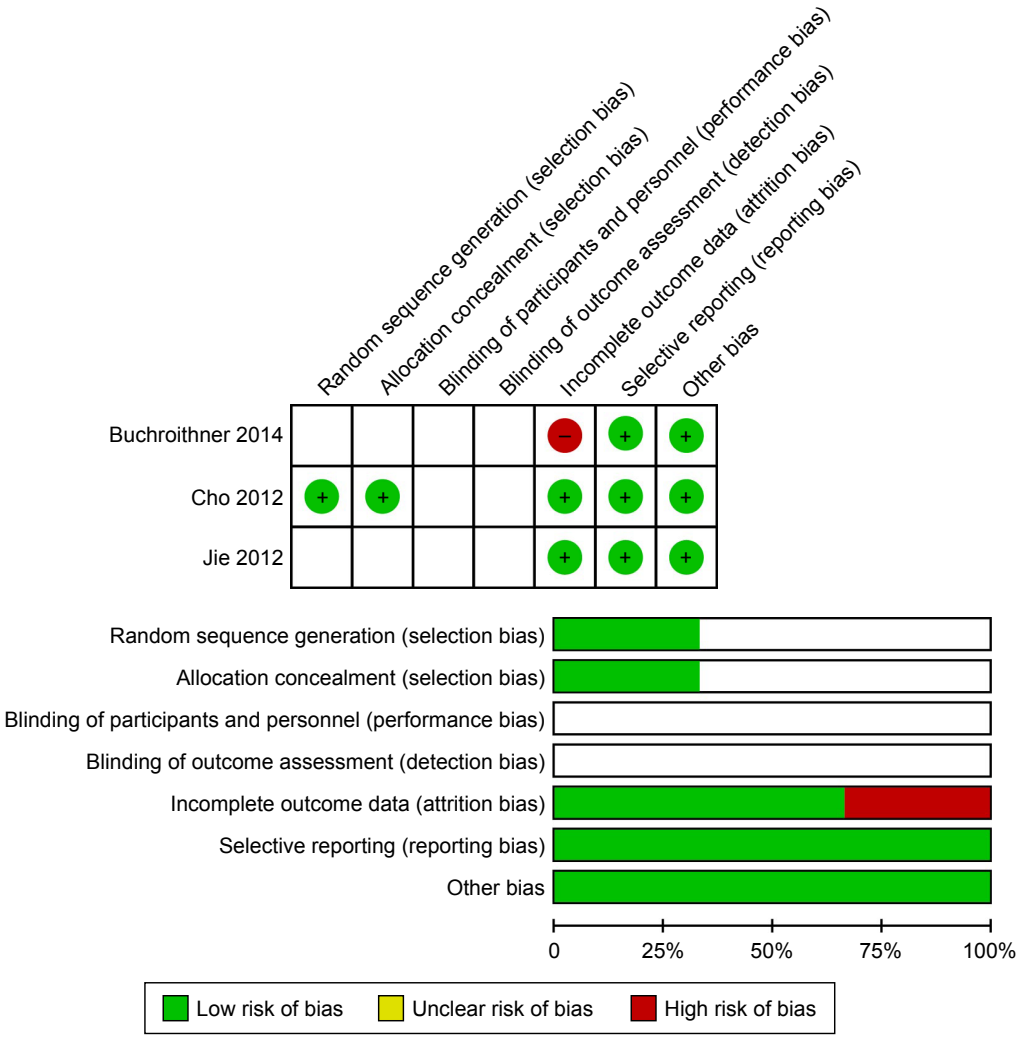

Figure 2 Risk of bias analysis for randomized clinical trials included.

Table 6 Risk of bias of non-randomized studies by NOS scale

Study	Year	Study design	Selection				Comparability	Outcome			Total score
			Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Yu et al[25]	2004	NRCT	*	*	*	*	**	*	*	*	9
Wheeler et al[23]	2004	NRCT	*	*	*	*	**	*		*	8
Yamanaka et al[24]	2005	NRCT	*	*	*	*	**	*		*	8
Liau et al[22]	2005	NRCT	*	*	*	*	**	*	*	*	9
Leplina et al[21]	2007	NRCT	*	*	*	*		*		*	6
Chang et al[28]	2011	Historical	*		*	*	**	*	*	*	8
Prins et al[27]	2011	Historical	*		*	*	*	*	*	*	7
Vik-Mo et al[26]	2013	Historical	*	*	*	*	**	*		*	8
Müller et al[30]	2015	Cohort	*			*		*	*	*	5
Batich et al[29]	2017	Historical	*		*	*	*	*	*	*	7

Notes: Cohort, cohort study; historical, historically controlled trial.
Abbreviations: NOS, Newcastle–Ottawa scale; NRCT, non-randomized controlled trial.

was found after deleting any of the studies, representatively shown in Figure 3 (data from 1-year OS), indicating that no individual study affected the pooled RR significantly.

Publication bias

Publication bias was assessed by Egger's plot and Begg's test regarding OS and PFS, when studies included were more than ten. Results indicated that no significant difference was found in publication bias regarding OS (Begg's test: P=0.853, Egger's test: P=0.451, as representatively shown in Figure 4 for 1-year OS).

Discussion

In this meta-analysis, we evaluated the efficacy of DCs in treatment of HGGs, particularly in terms of the OS, PFS, and AEs. Results indicated that DCs could significantly improve OS and PFS without serious AEs. In the subgroup analysis, DCs were found to be more preferable in NRS than in RCTs in both 1-year OS, 2-year OS, and 3-year OS analysis. Interestingly, no specific difference was found both in 1-year OS and 2-year OS regarding cycles, dosages or routes of injection. Most of the individual subgroups was consistent with the primary outcome. We also performed sensitivity and publication bias analyses to investigate the robustness and bias between studies. In contrast to previous systematic reviews,[10,11] we collected studies from different regions with different study designs and varied pulsing methods, dosages, cycles, and injection routes for DC administration. With these freshly updated retrievals, we suggest that DC vaccine is safe and effective in improving OS and PFS in HGG patients.

HGGs are some of the most aggressive and refractory brain tumors. Although intensive efforts have been made, the prognosis for HGGs still remains ominous. The poor success of current treatment might partially be due to the translational gap resulting from insufficient consideration of basic concepts of glioma biology in clinical trials.[32] One of the most important factors that affects the successful treatment of HGGs is the blood–brain barrier (BBB), which prevents the diffusion of anticancer drugs into the central nervous system (CNS).[33] Fortunately, DC vaccine provides a novel modality as immunotherapy, since CNS is no longer considered as an immune privileged site, but rather an actively regulated site of immune surveillance.[34] Similar to other leukocytes, DCs can transmigrate the BBB under multiple conditions via different pairs of receptors and ligands.[35] Our analysis further confirmed that DC vaccine was effective in prolonging the OS and PFS in HGG patients.

However, there is still a long way to go for DC vaccines to be standardized. As we summarized in this analysis,

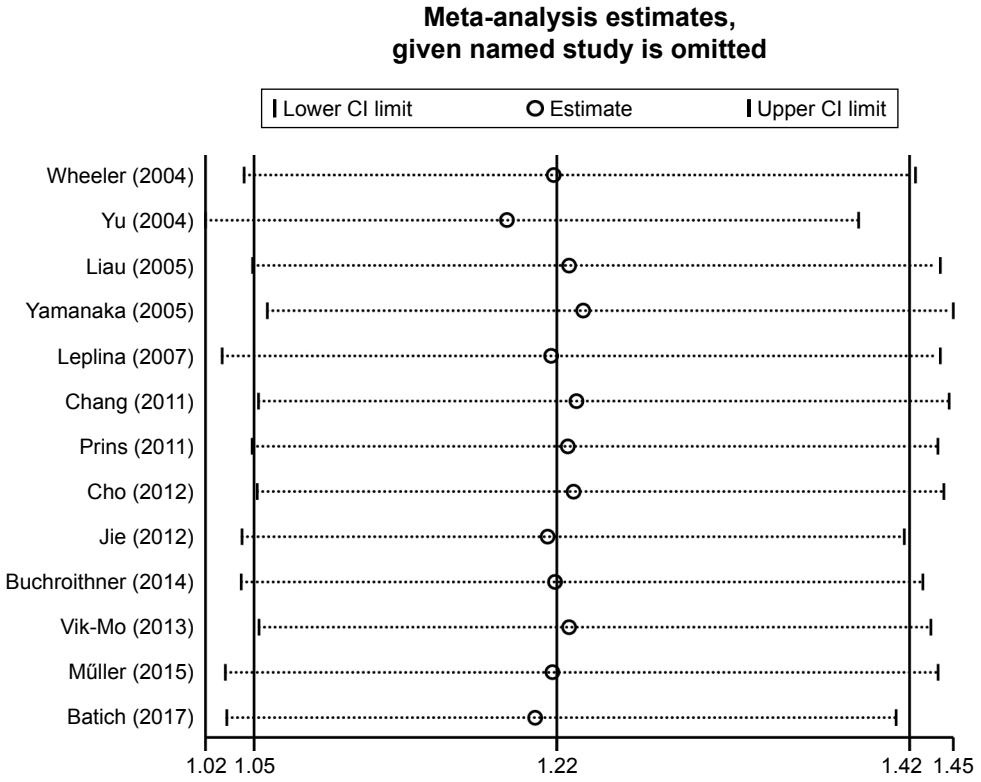

Figure 3 Sensitivity analysis for 1-year overall survival.

Tests for publication bias
Begg's test
Adj kendall's score (P-Q) =10
SD of score =16.39
Number of studies =13
z =0.61
Pr>|*z*| =0.542
z =0.55 (continuity corrected)
Pr>|*z*| =0.583 (continuity corrected)

Egger's test

Std_Eff |	Coef	Std Err	*t*	*P*>|t|	(95% CI)	
Slope |	0.076584	0.1561391	0.49	0.633	–0.2670757	0.4202438
Bias |	0.4379253	0.5602005	0.78	0.451	–0.7950676	1.670918

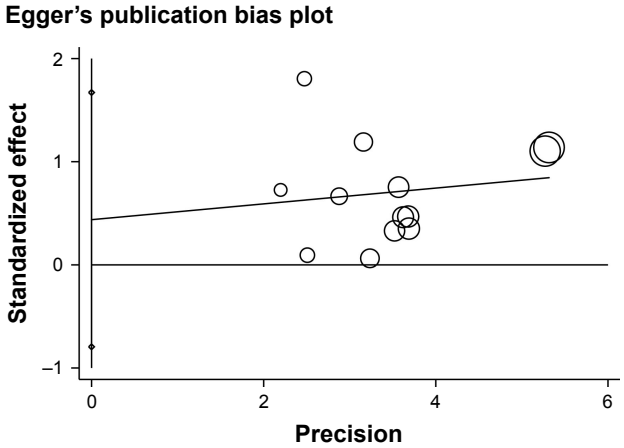

Figure 4 Publication bias analysis for 1-year overall survival.

DCs were prepared in multiple ways, then administered via different routes for varied cycles with a broad range of dosages. To be activated, DCs were pulsed with ATL, peptides, DNA constructs or through fusion of DCs with tumor cell lines.[36] From this meta-analysis, we could not determine which kind of activation of DCs was better than the others. The magnitude of antigen-specific cytotoxic T-lymphocyte responses to DC vaccination is determined by the migration of DCs to lymphoid tissues. However, the migration was greatly affected by the administration route of activated, mature DCs. A variety of injection routes has been investigated, including ID, SC, intravenous, intraperitoneal, intranodal (intralymphatic), and IT. But the optimal route of administration has yet to be determined, although intranodal injection offers the advantage of DCs not needing to migrate, as they are already in close proximity to T-cells in the lymph node.[36,37] From the data we collected, we could not make a suggestion for the route of DC administration in HGG patients. Neither could we come to a conclusion for the dosages or cycles to be applied.

Our study also had some limitations. Primarily, most of the studies included were NRS, although RCTs are well accepted as the gold standard for intervention studies.[38] Secondly, the basis for grouping patients in each study slightly differed, which could have affected the analysis of

OS and PFS in each study to some extent. Thirdly, although there was no statistical publication bias in the overall analysis, only papers published in English with full-text were included in this meta-analysis. This may have resulted in other eligible studies that were unpublished or reported in other languages being left out. In addition, the cohort study and some RCTs without clear report on randomization or allocation concealment, increased the risk of bias in this meta-analysis.

Conclusion

DC vaccine is safe and effective in reducing mortality and tumor recurrence for patients with HGGs. In the future, double-blind, randomized, placebo-controlled trials in Phase III with adequate follow-up would provide more information on the analysis of DC application in cancers.

Acknowledgment

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Author contributions

HY and YS designed the study, CL and TL collected the data, separately, which was confirmed by BZ and YZ. Data analysis was performed by CL and YS. The first manuscript was written by HY and approved by all the authors. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4–5
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5–6
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9,11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6–7
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11

Figure S1 (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8–11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8–11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	12
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	12–13
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	13–14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	14

Figure S1 PRISMA checklist.
Notes: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 6(7):e1000097. doi: 10.1371/journal.pmed1000097.[1] For more information, visit: www.prisma-statement.org.

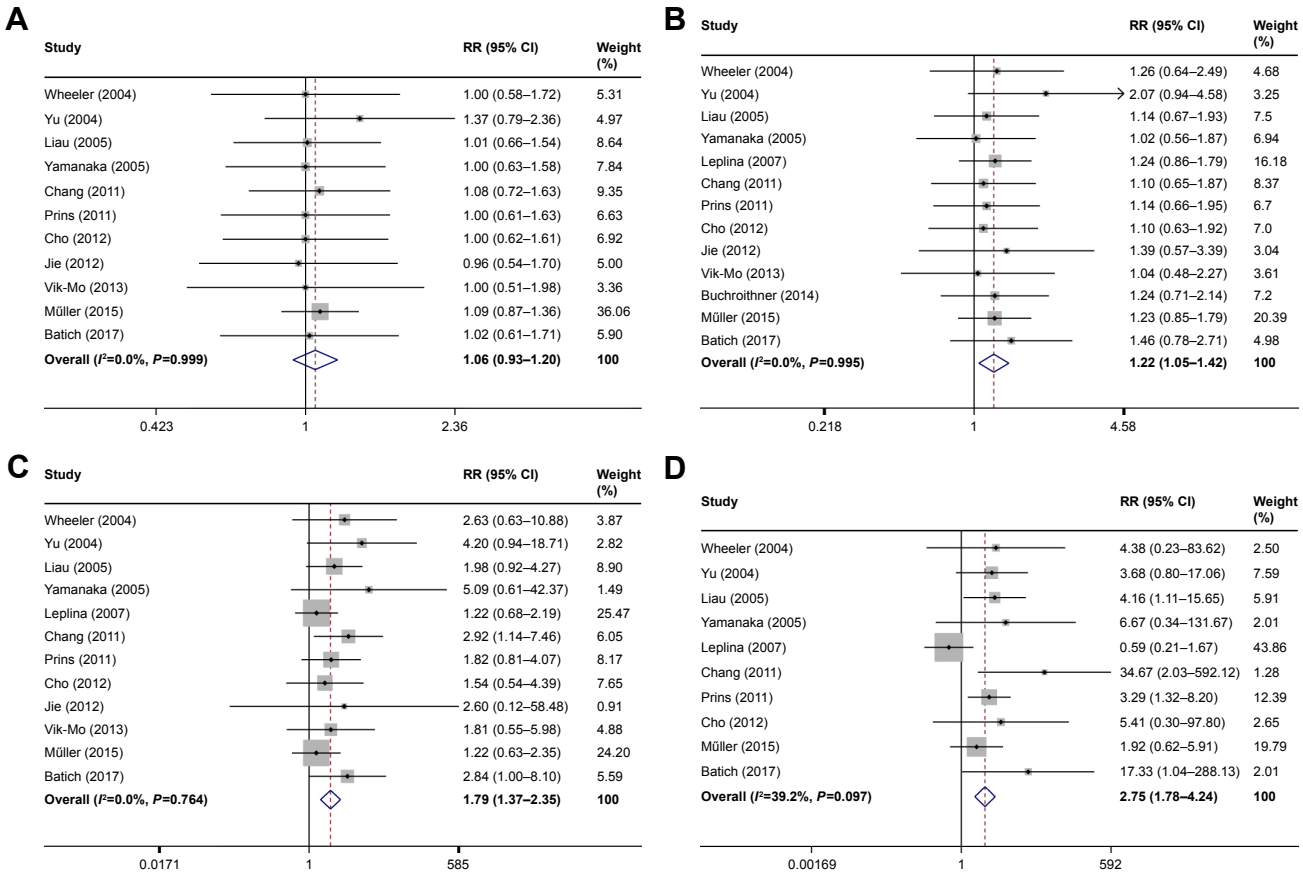

Figure S2 (*Continued*)

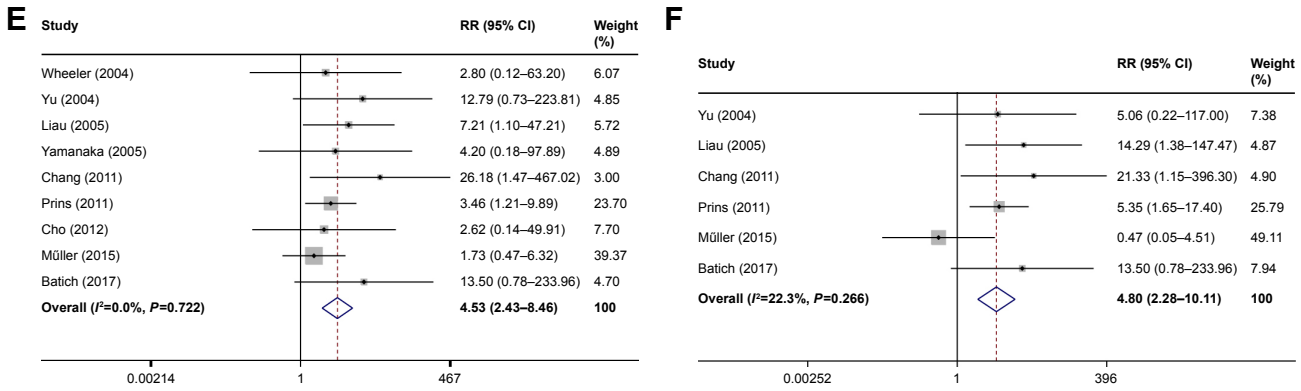

Figure S2 Forest plots for overall survival (OS) analysis of high-grade glioma patients treated with dendritic cells.
Note: (**A**) 0.5-year OS, (**B**) 1-year OS, (**C**) 2-year OS, (**D**) 3-year OS, (**E**) 4-year OS, (**F**) 5-year OS.

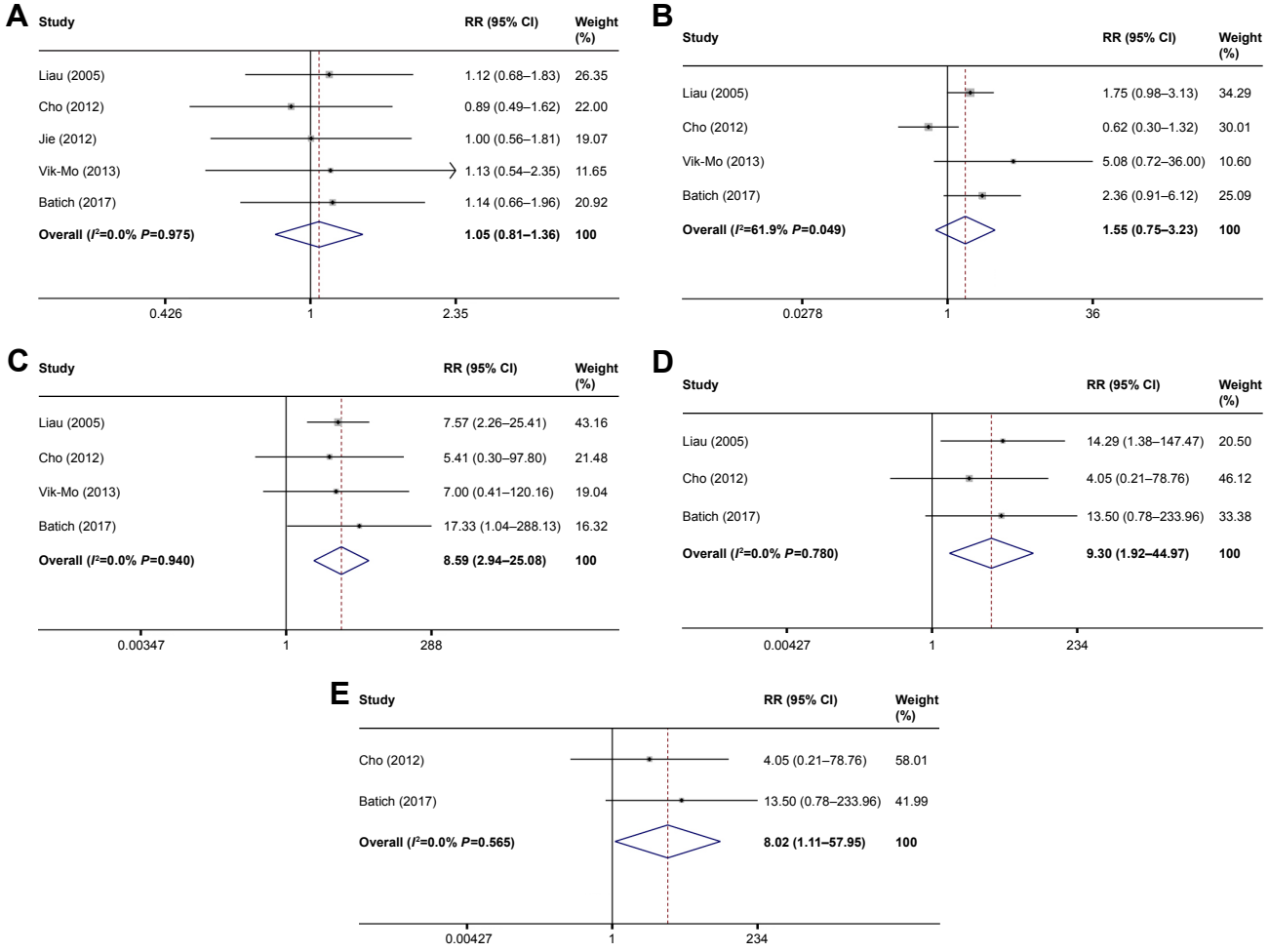

Figure S3 Forest plots for progression-free survival (PFS) analysis of high-grade glioma patients treated with dendritic cells.
Notes: (**A**) 0.5-year PFS, (**B**) 1-year PFS, (**C**) 2-year PFS, (**D**) 3-year PFS, (**E**) 4-year PFS. Weights are from random-effects analysis.

Reference

1. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 6(7):e1000097.