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Efficacy and safety of dendritic cell vaccines for patients with glioblastoma: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Dendritic cell (DC)-based vaccination has been suggested to be promising for glioblastoma. However, the evidence in randomized controlled trials (RCTs) is inconsistent. We aimed to systematically evaluate the efficacy and safety of DC vaccine for glioblastoma via a meta-analysis of RCTs.

Methods: Related randomized controlled trials (RCTs) were identified via a search of PubMed, Embase, and Cochrane's Library. We used a random-effect model to pool the results.

Results: Six phase II RCTs with 347 patients with newly diagnosed or recurrent glioblastoma that underwent conventional treatments were included. Compared to the control group with placebo or blank treatment, DC vaccine was associated with significantly improved overall survival in patients with glioblastoma (hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.49 to 0.97, p = 0.03) with moderate heterogeneity (p for Cochrane's Q test = 0.07, I^2 = 51%). A trend of improved progression-free survival was also detected in patients allocated to the DC vaccine group compared to those in the control group (HR: 0.76, 95% CI: 0.56 to 1.02, p = 0.07), with no significant heterogeneity (I^2 = 0%). Moreover, the incidence of adverse events was not significant between patients treated with DC vaccine or control (odds ratio = 1.52, 95% CI: 0.88 to 2.62, p = 0.14; I^2 = 0%).

Conclusions: Evidence based on phase II RCTs suggests that DC vaccine may improve the survival of patients with glioblastoma. Large-scale RCTs are needed to validate the findings and determine the optimal regimens for DC vaccine.

1. Introduction

Glioblastoma, a World Health Organization (WHO) stage IV glioma, is the most common type of glioma [1]. The current standard of care for patients with glioblastoma includes combined treatment with surgical resection, radiotherapy, and oral chemotherapy with temozolomide [2]. However, despite the above conventional therapies, the prognosis of patients with glioblastoma remains extremely poor, with a reported five-year survival of < 10% [3]. Therefore, novel effective treatment options are needed for glioblastoma.

Accumulating evidence from basic research has revealed that glioblastoma itself may elicit immune suppression, thereby leading to the escape of the tumor from the surveillance of the human immune system [4]. Accordingly, it has been proposed that active immunotherapy, which potentially interacts with the immune system of patients in order to initiate an immune response against the tumor cells, may be a novel effective treatment for cancers, including glioblastoma [5]. Among many cellular and cytokine components involved in cancer immune response, dendritic cells (DC) have been recognized to play an important role as antigen-presenting cells (APCs) in initiating immune responses [6,7]. Pilot clinical trials suggested that DC vaccination could be well tolerated and may improve survival in patients with glioblastoma, highlighting the potential of DC vaccines as an alternative novel therapy for the disease [8,9]. However, subsequent randomized controlled trials (RCTs) evaluating the efficacy and safety of DC vaccines for glioblastoma returned inconsistent results [10–15]. Some studies showed a significant improvement in survival following DC vaccination for patients with glioblastoma compared to the effect of conventional therapies [10,14,15], while other studies showed negative findings [11–13]. Due to the limited sample sizes included in previous RCTs, the possibility that some studies may be statistically unable to obtain a significant survival outcome cannot be ruled out. On the other hand, several meta-analyses have been performed on this topic [16–19]. However, previous meta-analyses included heterogeneous

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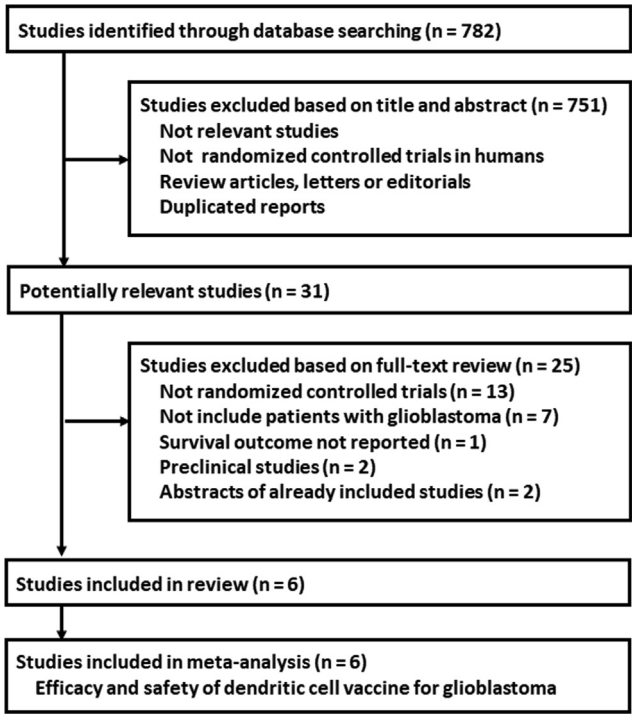

Fig. 1. Flowchart of database search and study identification.

patients with other high-grade glioma besides glioblastoma, such as anaplastic astrocytoma and oligodendroglioma, which makes the interpretation of the study results difficult [16–19]. Moreover, a substantial number of non-RCTs were included with RCTs, which leads to additional biases [16–19]. In addition, the previous meta-analyses only included studies before 2018 and some recently published RCTs have not been analyzed [13–15]. Therefore, we aimed to perform a meta-analysis of RCTs to systematically evaluate the efficacy and safety of DC vaccines for glioblastoma.

2. Materials and methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and the Cochrane Handbook for Systematic Review and Meta-analysis [20] were followed in designing, performing, and reporting the meta-analysis.

2.1. Search strategy

PubMed, Embase, and Cochrane's Library (Cochrane Center Register of Controlled Trials) electronic databases were searched for RCTs evaluating the efficacy and safety of DC-based vaccination in patients with glioblastoma on the basis of conventional therapy consisting of surgery, radiotherapy, and chemotherapy with temozolomide. The search keywords were: (1) "glioma" OR "glioblastoma multiforme" OR "high-grade glioma" OR "glioblastoma"; and (2) "dendritic". We limited the search to human studies, and no language restriction was applied. Reference lists of related articles and reviews were also screened manually. The final search was performed on November 18th, 2019.

2.2. Study selection

The inclusion criteria were: (1) full-length articles; (2) designed as parallel RCTs; (3) included patients with glioblastoma that underwent conventional treatments consisting of surgery, radiotherapy, and chemotherapy with temozolomide; (4) directly compared the efficacy and safety of DC-based vaccination with controls of placebo or blank

Table 1
Characteristics of the included RCTs.

Study	Design	Country	Patient characteristics	Trial Phase	Sample size	Mean age	KPS at baseline	Control treatment	DC treatment	Follow-up duration
					DC vs Control	years				Months
Jie et al. [11]	R, OL	China	Newly diagnosed GBM patients underwent S + R + TZM	II	13 vs 12	42	> 60	Blank	Autologous tumor lysates treated with DC (total: 10^6) via intradermal injection administered four times	24
Cho et al. [10]	R, OL	China	Newly diagnosed GBM patients underwent S + R + TZM	II	18 vs 16	54	> 70	Blank	Fusion of DC (total: 2 ~ $5x10^7$) and killed tumor cells via intradermal injection administered 10 times	33
Buchroithner et al. [12]	R, OL	Austria	GBM patients underwent S + R + TZM	II	19 vs 21	NA	NA	Blank	Autologous tumor lysates treated with DC via inguinal lymph node injection administered 10 times	18
Buchroithner et al. [13]	R, OL	Austria	Newly diagnosed GBM patients underwent S + R + TZM	II	39 vs 42	54	NA	Blank	Autologous tumor lysates treated with DC (total: 2 ~ $5x10^7$) via inguinal lymph node injection administered 10 times	12
Yao et al. [14]	R, DB, PC	China	Newly diagnosed or recurrent GBM patients underwent S + R + TZM	II	22 vs 21	49	> 60	Saline	Glioblastoma stem cell-like antigens treated with DC (total: 1 ~ $3x10^7$) via intradermal injection administered 3 times	24
Wen et al. [15]	R, DB, PC	the US	Newly diagnosed GBM patients underwent S + R + TZM	II	81 vs 43	58	> 70	Unpulsed DC	DC pulsed with synthetic peptide epitopes targeting GBM-associated antigens (total: $4.4x10^7$) via intradermal injection administered four times	18

R, randomized; OL, open-label; DB, double-blinded; PC, placebo-controlled; S, surgery; R, radiotherapy; TZM, temozolomide; GBM, glioblastoma; DC, dendritic cell dendritic cell; KPS, Karnofsky performance scale.

Table 2
Quality evaluation of the included RCTs via the Cochrane's Risk of Bias Tool.

	Random sequence generation	Allocation concealment	Blinding in performance	Blinding in outcome detection	Incomplete outcome data	Reporting bias	Other bias	Total
Jie et al. [11]	Unclear	Unclear	High	High	Low	Low	Unclear	2
Cho et al. [10]	Low	Low	High	High	Low	Low	Low	5
BBuchroithner et al. [12]	Unclear	Unclear	High	High	Low	Low	Unclear	2
Buchroithner et al. [13]	Unclear	Low	High	High	Low	Low	Low	4
Yao et al. [14]	Low	Unclear	Low	Low	Low	Low	Low	6
Wen et al. [15]	Unclear	Unclear	Low	Low	Low	Low	Low	5

treatment; and (5) reported the efficacy outcome as overall survival (OS) and/or progression-free survival (PFS) and the safety outcome of any adverse events. Reviews, preclinical studies, non-RCTs, and studies that did not report related outcomes were excluded from the current study.

2.3. Data extraction and quality assessment

Two authors performed the literature search, data extraction, and quality assessment independently. If discrepancies occurred, consensus with the corresponding author was indicated. Extracted data included study information (first author, publishing year, and study country), study design (blind or open-label), characteristics of patients with glioblastoma (number of patients in each group, age, and Karnofsky performance scale [KPS] at baseline), regimen of controls (blank treatment or placebo), and DC-based vaccination characteristics (DC cell preparation, routes, dosages, and treatment durations). The seven-domain Cochrane risk of bias tool was applied to evaluate the quality of the studies [20]. This instrument includes quality judgment according to the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential threats to validity.

2.4. Statistical analysis

We used the hazard ratio (HR) and 95% confidence intervals (CIs) as the effect measure for the time-to-event outcomes of OS and PFS. Survival data were directly extracted from tables or text. If these data were only shown in Kaplan–Meier curves, Engauge Digitizer version 10.4 was used to extract the data (free software downloaded from http://sourceforge.net) and the corresponding HR and 95% CIs were estimated via a validated method from Tierney et al. as previously proposed [21]. Dichotomous data were analyzed using odds ratios (ORs) with 95% CIs. Cochrane's Q test was applied to evaluate the heterogeneity among the included studies, and significant heterogeneity was considered for $P < 0.10$ [22]. The I^2 statistic, which reflects the percentage of variation across studies due to heterogeneity rather than chance, was also calculated to indicate the heterogeneity [23]. An $I^2 > 50\%$ indicated significant heterogeneity among the trials. Pooled analyses were calculated using a random-effect model because this model was considered to incorporate the potential heterogeneity among the included RCTs and therefore could retrieve a more generalized result [20]. Publication bias was estimated by visual inspection for the symmetry of the funnel plots, complemented with Egger's regression asymmetry test [24]. Statistical significance was defined as two-tailed P values < 0.05. The RevMan software (Version 5.1; Cochrane, Oxford, UK) was used for statistical analysis.

3. Results

3.1. Search results

A total of 782 articles were identified through the database search, and 751 were excluded based on the screening of titles and abstracts, mostly because they were not relevant to the purpose of the studies. Of the 31 articles that were potentially relevant, 25 articles were excluded because 13 were not RCTs, seven did not include patients with glioblastoma, one did not report survival data, two were preclinical studies, and the other two were repeated reports of already included RCTs. Finally, six RCTs were included [10–15] (Fig. 1).

3.2. Study characteristics

Overall, this meta-analysis included six phase II RCTs with 347 patients with newly diagnosed or recurrent glioblastoma that underwent conventional treatments [10–15]. The characteristics of the included RCTs are summarized in Table 1. All of the studies were published in English between 2012 and 2019. Three RCTs were performed in China [10,11,14] two in Austria [12,13], and the remaining one in the US [15]. All of the RCTs were phase II clinical trials. The sample sizes of the included studies varied from 25 to 124, with the mean age of the patients ranging from 42 to 58 years. The baseline KPS for the included patients was > 60. In four studies, DC was prepared using autologous tumor lysates [11–13] or killed tumor cells [10], while the other two involved DC vaccination with glioblastoma stem cell-like antigens [14] or pulsed DC with synthetic peptide epitopes targeting glioblastoma-associated antigens [15]. The total amount of DC cells was 1×10^6–5×10^7, which were divided into 3–10 intradermal or inguinal lymph node injections. The control was blank treatment in four studies [10–13], or placebo with saline [14] or untreated DC [15] in two studies. The follow-up durations varied from 12 to 33 months.

3.3. Study quality

Details of quality assessment for the included studies according to the Cochrane's Risk of Bias Tool are listed in Table 2. Briefly, two of the included RCTs were double-blinded studies [14,15], while the rest were open-label [10–13]. Details of random sequence generation were reported in two studies [10,14]. Measures for allocation concealment were also applied in two studies [10,13]. All studies reported details of withdrawals and dropouts.

3.4. Efficacy outcome

Details of the median survival and PFS for patients allocated into each study arm in the included RCTs are provided in Table 3. Six RCTs [10–15] with 347 patients reported the effect of DC vaccine on OS in patients with glioblastoma. Pooled results with a random-effect model showed that the DC vaccine was associated with significantly improved OS in patients with glioblastoma as compared with controls (hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.49 to 0.97, p = 0.03;

Table 3
Characteristics of the included RCTs.

Study	Sample size (DC/ Control)	Median survival	0.5-year PFS	1-year PFS	2-year PFS	3-year PFS	4-year PFS	Adverse events
		months	Patients, %	Patients, %	Patients, %	Patients, %	Patients, %	Patients
Jie et al. [11]	13	17.0	12, 92.3%	NR	NR	NR	NR	3 (2 fevers and 1 red papules)
	12	10.5	11, 91.7%	NR	NR	NR	NR	0
Cho et al. [10]	18	31.9	12, 66.7%	7, 38.9%	3, 16.7%	2, 11.1%	2, 11.1%	2 (1 transient abnormal liver function and 1mild lymphopenia)
	16	15.0	13, 81.3%	13, 81.3%	0	0	0	1 (1 scalp infection)
Buchroithner et al. [12]	19	14.6	NR	NR	NR	NR	NR	NR
	21	12.7	NR	NR	NR	NR	NR	NR
Buchroithner et al. [13]	39	18.8	26, 66.7%	11, 28.2%	2, 5.1%	1, 2.6%	1, 2.6%	18 (7 thrombopenia, 1 lymphopenia, 2 leucopenia, 2 rash, 3 fatigue, 2 headache, and 1 nausea)
	42	18.9	30, 71.4%	12, 28.6%	2, 4.8%	0	0	12 (2 thrombopenia, 2 leucopenia, 1 rash, 1 fatigue, 2 headache, 3 VTE events, and 1 ICH)
Yao et al. [14]	22	17.3	17, 77.2%	3, 13.6%	0	0	0	2 (1 fever and 1 erythema)
	21	10.7	14, 66.7%	3, 14.3%	0	0	0	0
Wen et al. [15]	81	17.0	56, 69.1%	40, 49.4%	10, 12.3%	0	0	47 (14 nervous system disorder, 6 administration site conditions, 3 fatigue, 1 musculoskeletal disorder, 4 investigations, 6 blood disorders, 2 infections, 3 metabolic disorders, and 8 skin disorders)
	43	15.0	26, 60.4%	12, 28.5%	0	0	0	25 (7 nervous system disorder, 5 administration site conditions, 3 fatigue, 3 musculoskeletal disorder, 4 blood disorders, and 3 infections)

GBM, glioblastoma; DC, dendritic cell dendritic cell; PFS, progression free survival; NR, not reported; VTE, venous thromboembolic; ICH, intracranial haemorrhage.

Fig. 2A) with moderate heterogeneity (p for Cochrane's Q test = 0.07, I^2 = 51%). Meta-analysis of five RCTs [10,11,13–15] showed a trend of improved PFS in patients allocated to the DC vaccine group as compared with the control group (HR: 0.76, 95% CI: 0.56 to 1.02, p = 0.07; Fig. 2B) with no significant heterogeneity (I^2 = 0%).

3.5. Safety outcome

Details of the adverse events in patients allocated into each study arm in the included RCTs are presented in Table 3. The most frequently reported adverse events related to DC vaccine were fever and rash at the injection sites, which were mild. Meta-analysis of five RCTs [10,11,13–15] showed that the overall incidence of adverse events was not significant between patients treated with DC vaccine or control (OR = 1.52, 95% CI: 0.88 to 2.62, p = 0.14; I^2 = 0%; Fig. 3).

3.6. Publication bias

The funnel plots for the meta-analyses of OS, PFS, and incidence of adverse events are shown in Fig. 4A-4C, respectively. These plots were symmetrical on visual inspection, indicating a low chance of publication biases. We did not perform Egger's regression tests due to the limited number of studies included.

4. Discussion

In this meta-analysis of RCTs, we found that DC vaccination was associated with significantly improved OS (HR = 0.69) and a trend of improved PFS (HR = 0.76, p = 0.07) in patients with glioblastoma who underwent combination therapy consisting of surgical resection, radiotherapy, and chemotherapy with temozolomide. Moreover, the incidences of adverse events were not significantly different in patients allocated to the DC vaccine and control groups. Taken together, these results demonstrated that DC vaccines may improve the survival of patients with glioblastoma. Large-scale RCTs are needed to validate the findings and determine the optimal regimens for DC vaccines.

This meta-analysis has the following strengths compared to previous meta-analyses [16–19]. Firstly, we only included patients with glioblastoma that underwent conventional treatment, and the homogeneity of the study population makes the results of the meta-analysis more clinically relevant. Secondly, only RCTs evaluating the safety and efficacy of DC vaccines were included, which eliminated the risk of potential confounding effects on the outcomes from unmatched patient or study characteristics in non-RCTs. Thirdly, an up-to-date meta-analysis with recently published RCTs was performed including 347 patients with newly diagnosed or recurrent glioblastoma. The relatively large sample size in the meta-analysis reduced the risk of statistical inadequacy, which may lead to negative findings. Since the results of the randomized phase III clinical trials evaluating the clinical efficacy of DC vaccines in patients with glioblastoma remain unreported [25], our meta-analysis, by pooling the results of updated phase II RCTs, support the efficacy of DC vaccines as alternative treatments for patients with glioblastoma on the basis of conventional therapies, which is likely associated with improved survival in these patients.

Immune suppression has been recognized as a common feature of tumors in the central nervous system because of the presence of the blood-brain barrier and lack of classic lymphatic vessels. Additionally, glioblastoma has been shown to elicit an immune suppressive environment with various molecular mechanisms such as the activation of signal transducer and activator of transcription 3 (STAT3) and its transcriptionally regulated product hypoxia inducible factor (HIF)-1α [26] as well as the upregulation of *LGALS1* encoding Galectin-1 [27]. Interestingly, it has been observed that immunosuppression is enhanced in therapy-exposed glioblastoma multiforme tumor cells compared to those not exposed to chemotherapy or irradiation [28], highlighting the potential efficacy of immunotherapy for glioblastoma, particularly for

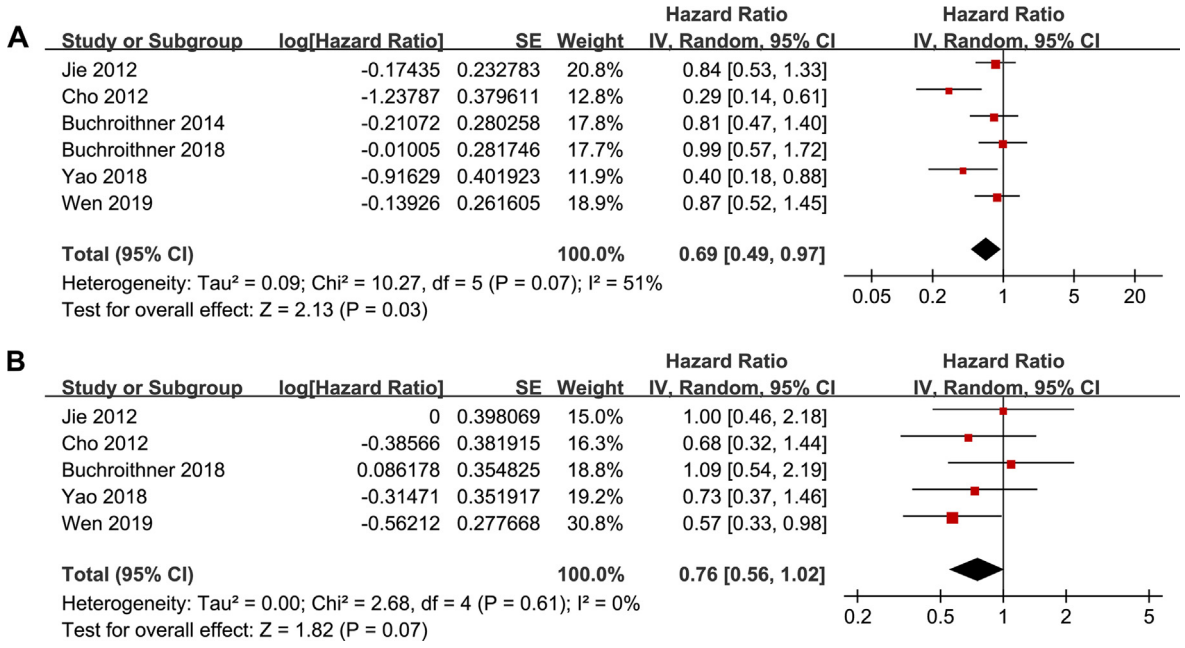

Fig. 2. Forest plots for the meta-analyses comparing the efficacy outcomes between DC-based vaccination and control for glioblastoma; A, overall survival; and B, progression-free survival;

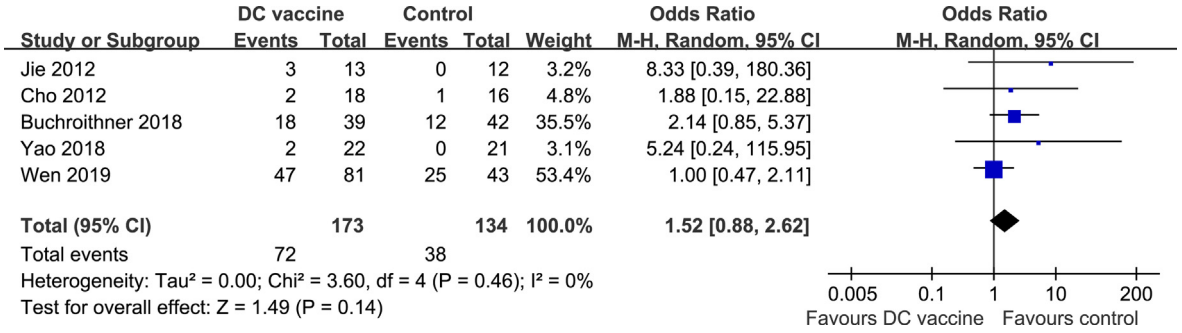

Fig. 3. Forest plots for the meta-analyses comparing the overall incidence of adverse events in patients with glioblastoma allocated to DC-based vaccination and control groups;

individuals that have already received conventional therapies. As essential APCs for the adaptive immune system, DCs engulf and process tumor antigens and express them on the surface of DCs for the presentation to CD8+ and CD4+ T-lymphocytes, subsequently initiating an active immune response to infection and cancers [20]. It is worth noting that although all of the included studies used DC vaccines to treat glioblastoma, different strategies were employed for DC preparation and activation, including killed tumor cells [11], autologous tumor lysates [10,12,13], glioblastoma stem cell-like antigens [14], and synthetic peptide epitopes targeting glioblastoma-associated antigens [15]. The relative efficacy of these DC vaccine preparation methods and influential factors should be evaluated in the future. Interestingly, since Human Cytomegalovirus (CMV) antigens have been identified in glioblastomas but not in the normal brain, a recent study showed that vaccination with CMV phosphoprotein 65-loaded DC may be an alternative effective treatment for glioblastoma, although survival analyses have not been performed yet [29]. Future studies are needed to determine the optimal preparation protocol and regimens for DC-based vaccination in glioblastoma.

Our study has limitations which should be considered when interpreting the results. Firstly, a limited number of RCTs were available. The RCTs typically had small sample sizes, and we did not have access to the data for individual patients. Therefore, we were unable to determine the potential influences of the study characteristics on the outcomes. For example, one of the included studies found that the mutation status of isocitrate dehydrogenase (IDH1/2) and telomerase reverse transcriptase (TERT) may affect the therapeutic efficacy of DC vaccination on survival in patients with glioblastoma [30]. However, we were unable to validate the finding at a meta-analysis level since the mutant states of the above enzymes were not reported in other studies. In addition, whether the therapeutic efficacy of DC vaccination on survival is consistent in patients with recurrent and newly diagnosed GBM remains to be determined. We were unable to resolve this issue since four of the RCTs included newly diagnosed GBM only [10,11,13,15], while the other two included a mixed population of patients with recurrent and newly diagnosed GBM [12,14], without providing the stratified data. Future RCTs with adequate sample sizes are warranted to evaluate the potential influence of the study characteristics on the effects of DC vaccination on survival outcomes. Secondly, the optimal regimens and protocols for DC vaccines in patients with glioblastoma remain to be determined, such as the preparation strategy, amount of cells, injection routes, and intervals [6]. These factors may all affect the clinical efficacy of the DC vaccine. Finally, four of the included RCTs were open-label [10–13] and some of the RCTs had poor quality [10,12], which may also lead to potential bias. Our results need to be validated in high-quality RCTs in the future.

The results of our meta-analysis based on phase II RCTs showed that DC vaccines are well tolerated and may improve the survival of patients

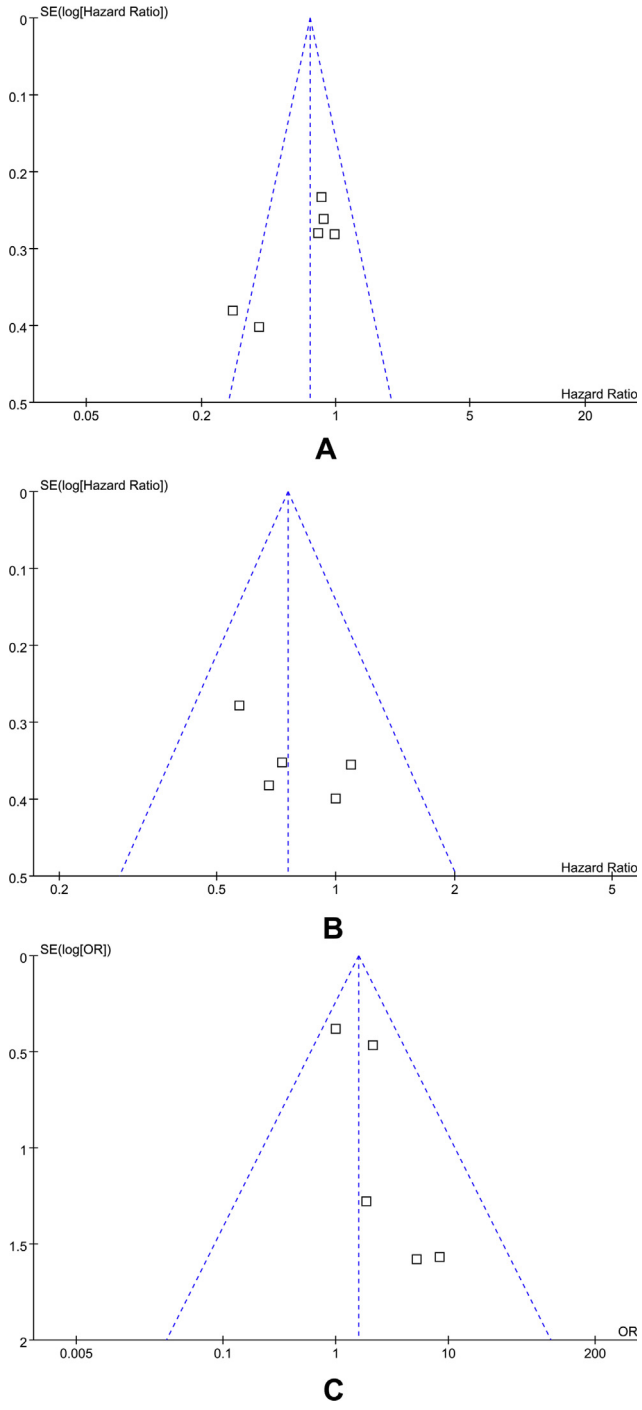

Fig. 4. Funnel plots for the meta-analyses; A, overall survival; B, progression-free survival; and C, adverse events; the funnel plots were constructed as scatter plots in which the treatment effects estimated from individual studies (HRs or ORs) on the horizontal axis are plotted against a measure of study precision (SE of log [HR] or SE of log [OR]) on the vertical axis. The plot resembles a symmetrical inverted funnel because the estimates of the treatment effect from smaller studies are scattered more widely at the bottom of the graph, with the spread narrowing with increasing precision among larger studies, which indicated no significant publication bias.

with glioblastoma. Nonetheless, challenges remain in performing phase III RCTs with regard to the optimization of DC migration and DC vaccine delivery, refinement of antigen selection, standardization of the maturation process, and determination of ideal adjuvant therapies. A recent study [31] in advanced high-grade ovarian serous carcinoma showed that DCs pulsed with personalized peptides generated from an individual patient's tumor-specific antigens may be important to improve the generation of a peptide-specific immune response against the tumor. The rate of successful migration of injected DCs to lymph nodes is less than 5% according to previous studies. Accordingly, in vivo targeting of DCs that use antibodies to target DC-specific cell receptors and thereby facilitate subsequent trafficking antigens to DCs may be an effective strategy [32]. As for the adjuvant therapies for DC vaccine, recent studies showed that the maturation of dendritic cells by maitake α-glucan YM-2A isolated from Grifola frondosa was associated with an enhanced anti-cancer effect from dendritic cell vaccination [33]. Additionally, checkpoint inhibitors such as anti-CTLA4 (Ipilimumab) have been proposed to confer synergetic anticancer efficacy with cancer vaccines [34], demonstrating that combination therapy may be important to improve the efficacy of immunotherapy in glioblastoma. The interim results in the first Phase III clinical trial of autologous tumor lysate pulsed dendritic cell vaccine (DCVax-L) in newly diagnosed glioblastoma patients were recently published and showed the promising feasibility of integrating DC vaccine into standard therapy, with a potential survival benefit [25]. The final results from these Phase III clinical trials are needed to validate the potential survival benefits of DC vaccine in patients with glioblastoma.

5. Conclusions

In conclusion, our meta-analysis based on phase II RCTs suggests that DC vaccines may improve the survival of patients with glioblastoma. Large-scale RCTs are needed to validate the findings and determine the optimal regimens for DC vaccination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.106336.

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