BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048975
Article Type:	Original research
Date Submitted by the Author:	13-Jan-2021
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Keywords:	NEUROSURGERY, ONCOLOGY, Head & neck tumours < ONCOLOGY

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Bevacizumab may prolong progression-free survival of gliomas: a systematic review and meta-analysis

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Keywords： glioma,progression-free survival,Bevacizumab

Number of words:2699

ABSTRACT

Objective**:** This study evaluated the efficacy and safety of bevacizumab in patients with glioma.

Design**:** Systematic review and meta-analysis.

Data sources**:** The data were collected using online search criteria from the databases like PubMed, Embase, The Cochrane Library, OVID , CNKI, and CBM database rom inception up to April 2020.

Intervention**:** Bevacizumab (BEV) and other interventions.

Primary and secondary outcome measures**:** The main indicators included progression-free survival rate and overall survival rate, and the secondary indicators were adverse reactions.

Results: A total of 10 clinical center trials were included in this study for meta-analysis, including 2392 patients . The results of the meta-analysis showed that the median progression-free survival rate of the BEV group (PFS) was significantly higher than that of the Non-BEV group (P<0.00001). When compared with the PFS rate of each stage, the PFS rate of the BEV group was 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03). The PFS of the BEV group was higher than that of Non-BEV group at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47). At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), the PFS of the Non-BEV group was lower than that of the Non-BEV group.Moreover, we have compared overall survival rate and the five common adverse reactions, including hypertension ,hemorrhage , and cerebral hemorrhage , Proteinuria and thromboembolism .

Conclusion: BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the high incidence of adverse events caused by long-term use of BEV. More prospective studies are needed to verify it in the future.

Strengths and Limitations of this study

1. We used the Cochrane criteria to assess the risk of bias.
2. The heterogeneity was explored by sensitivity, sub-group.
3. the quality of included studies was largely mod-erate to high.
4. The preoperative symptoms and the scope and degree of surgical resection are not taken into account.

INTRODUCTION

Brain glioma (High-Grade Glioma, HGG) is the most common primary intracranial tumor, accounting for about 27% of central nervous system tumors and 80% of intracranial malignant tumors[1]. The median survival time reported with brain glioma is 14-16 months[2]. The Surgical intervention combined with radiotherapy and chemotherapy are often followed for treatment of such cases, but because of its high invasive nature, it often relapses in a short time with poor prognosis. The emergence of temozolomide has considerably delayed the development of glioma to some extent, but the survival rate and quality of life of patients are still very low. Therefore, looking for better drugs to prevent and delay the postoperative recurrence of glioma has become the focus of current research. In recent years, more and more studies have shown that malignant glioma is the tumor with the highest degree of vascularization[3]. The nature of proliferation is characterized by obvious proliferative vascular lumen and with abnormal

proliferation of neovascularization which participates in the construction of tumor microenvironment[4]. It is closely related to the growth, invasion, and metastasis of the tumor, and positively correlated with the extent of malignancy and prognosis of the tumor. Recently, the unique biological characteristics of gliomas indicated that angiogenic factors may play an important role in its treatment and have become the focus of research.

Humanized anti-vascular endothelial growth factor monoclonal antibody-bevacizumab[5], as a representative drug of anti-angiogenic therapy, was approved for recurrent glioblastoma by FDA in 2009[6] and is listed in China in 2010 by CFDA. According to the radiological response rate, bevacizumab has been approved for recurrent glioblastoma in the United States and many other countries[7,8]. Although bevacizumab (BEV) has become an important part of HGG therapy, the safety and long-term efficacy of BEV are not clear. Therefore, we conducted a clinical meta-analysis to evaluate the safety and adverse reactions of BEV in patients with HGG, in order to provide a reference for clinical application.

METHODS

This study was mainly based on the literature research, and hence there was a requirement for ethical identification.

Search strategy

We collected all the clinical experimental studies of anti-angiogenic therapy in the treatment of gliomas, retrieved through a database search including PubMed, Embase, The Cochrane Library, OVID , CNKI, and CBM , from the establishment of the database to April 2020. The search strategy followed included a combination of subject words and free words, and the retrieval strategy was determined after several pre-searches. The main search words included: "glioma", "angiogenesis inhibitors", "vascular endothelial growth factors", "VEGF", and "clinical study". Additionally, we also manually searched the reference list of all articles on this topic to check and enhance the retrieval of other related publications. All search results are evaluated according to the (PRISMA) statement of "preferred reporting items for systematic review and meta-analysis".

Selection criteria

Studies were included if they fulfilled the following criteria: (1) Study subjects: the participants were patients of any age, whose histology was confirmed to be HGG. They may have undergone any form of surgery to achieve histological diagnosis (biopsy or

resection); (2) Study type: The clinical control study; (3) Intervention: BEV in bevacizumab group must include bevacizumab, which can be used alone or in combination with multiple drugs. The control group (Non-BEV) refers to treatment that does not include anti-angiogenesis, which can be placebo or supportive therapy, or active intervention (such as chemotherapy). (4) Outcome indicators: included in accordance with the following arbitrary outcome indicators: ① main indicators: progression-free survival (PFS)rate, defined as the time from randomization to death or disease progression of any cause, and overall survival(OS) rate, defined as the time from randomization to death. ② key indicators: adverse events classified according to the World Health Organization (WHO) or the General terminology Standard of the National Cancer Institute (NCI-CTCAE (CTCAE2017)), including the percentage of treatment-related deaths.

Studies were excluded if they fulfilled the following conditions: Non-clinical control studies, incomplete abstract information, conference papers, reviews, and case reports. In addition, the literature of repeated publication and incomplete data that cannot extract valid data should also be excluded.

Data extraction

Literature screening, data extraction, and cross-checking were carried out by two independent researchers according to the initial inclusion and exclusion criteria, and if there were any differences, it was discussed or judged with the assistance of a third person, and contact and supplement the missing data with the author as far as possible. During the literature screening, the title and the abstract were read initially, and after excluding the obviously irrelevant literature, the full text was read to determine whether to include it or not. Upon matching the inclusion criteria of requirements, the following contents were extracted: (1) the basic information, including title, author, published country, publication date, research type; (2) study subjects, including the number of cases in each group, average age; (3) interventional factors, including the specific details of exposure factors, follow-up time, etc.; (4) the outcome indicators.

Quality assessment

Using the Cochrane collaboration tool, the risk of bias in individual studies was assessed from seven aspects (sequence generation, allocation hiding, uninformed participants and people, incomplete outcome data, selective reports, and other biases and risks) [9]. Finally, each project was evaluated at three levels: low risk, unclear, and high risk. The two authors conducted independent quality assessments and any

differences among them were resolved through discussions with a third research expert.

Statistical analysis

Analysis of outcome index

PFS, OS, and adverse reactions were analyzed by Meta with RevMan5.1 software. The data were counted by risk ratio (hazard ratio; HR) and odds ratio (Odds ratio; OR). The interval estimation was expressed by 95%CI, and the test level of the effect quantity was $\alpha = 0.05$.

Heterogeneity analysis

The heterogeneity among the included results was analyzed by using the "I^2" (the level is $\alpha = 0.1$a). Simultaneously, combined with I^2 to quantitatively judge the size of heterogeneity, stata15.1 was used for sensitivity analysis, and the method of examining the influence of a single study was used to eliminate them one by one. The consistency of the results obtained after the above transformation shows that the results of Meta-analysis were stable, otherwise, they were regarded as unstable. Publication bias was detected by the funnel chart method.

RESULT

Literature screening

A total of 1108 related literature were obtained in the initial examination. After screening the literature one by one, a total of 1123 patients were included in 10 clinical studies[10-19]. The database and the number of documents retrieved are as follows: PubMed (nasty 259), The Cochrane Library (nasty 153), EMbase (nasty 155), CNKI (nasty 118), CBM (nasty 358), WangFang (nasty 65). The flow chart and the results of literature retrieval are shown in figure 1.

The basic characteristics of the inclusion study

For the inclusion study, the basic information for inclusion is completed using pre-developed forms (Tables 1, 2).

Table 1: basic information for inclusion in the study

Study	State	Research type	Cases (experimental/ control)	Ages(experimental / control)	Follow-up time	Outcom

Olivier L. Chinot, M.D[2014[10]]	France	RCT	458/463	20–84/18–79	The last patient was hospitalized for 17 months.	1and2year survival rates 、 safety and quality of life、PFS 、OS
Qianru Zhao[2016[11]]	China	RCT	25/24	24–71/27–	The median follow-up time was 7.9 months	disease control rate 、 median survival time、OS 、PFS
Ulrich Herrlinger[2016[12]]	Germany	RCT	116/54	25–78/26–78	Long-term follow-up until death	PFS–6、PFS、OS
Mark R.Gilbert 2016[13]	Germany	RCT	320/317	>18	6 cycles	OS、PFS
Clara Chen 2014[14]	America	Non-RCT	57/79/23	30–77/24–82/19-78	>1year	OS、PFS
Hualong Li [2020[15]]	China	RCT	31/31	18–70/19–69	4 months	PFS6、DCR、Adverse reaction
Zhixian Zhang 2018[16]	China	RCT	20/20	24–74	5. 2–18months	PFS6、OS12

Jiaqi Wang[2013][17]	China	RCT	27/27	53.6 ±9.7 /54.7±8.8	6months-2years	RR、DCR、Adverse reaction	
Albert Lai[2010][18]	America	RCT	70/110	31.3-75.8/ 20.5-90	>42months	OS、PFS、Adverse reaction	
B.Chauffert[2014][19]	Britain	RCT	60/60	43-69/43-71	6 months	OS、PFS、Adverse reaction	

Table 2: basic characteristics of the inclusion study

Study	Male	Female	Open biopsy	Partial resectio	Complete resection	experimental/ control
Olivier L. Chinot, M.D[2014]	282 (61.6) /298 (64.4)	176 (38.4) /165 (35.6)	60 (13.1) /44 (9.5)	210 (45.9) /223 (48.2)	188 (41.0) /196 (42.3)	Bevacizumab+ RT-TMZ/ Placebo+RT-TMZ
Qianru Zhao[2016]	14/12	11/12	/	15/16	10/8	BEV+TMZ/TMZ
Ulrich Herrlinger[2016]	80(69.0) /34(63.0)	36(31.0) /20(37.0)	0/2(3.7)	58(50.0)/27(50.0)	58 (50.0)/25 (46.3)	BEV+IRI/TMZ
Mark R.Gilbert[2016]	/	/	/	/	/	Bevacizumab/ Placebo

Clara Chen 2014	30(53)/45(57)/15(65)	57/79/23 27(47)/34(43)/8(35)	34(60)/44(56)/14(61)	20(35)/33(42)/9(39)	3(5)/2(2))/0(0)	Bevacizumab monotherapy /Bevacizumab combination /Nonbevacizumab
Hualong Li[2020]	19/18	12/13	/	/	/	TMZ+BEV/TMZ
Zhixian Zhang 2018	22	18	/	18	22	BEV+TMZ/ Gamma knife +TMZ/
Jiaqi Wang[2013]	16/14	11/13	/	/	/	TMZ+BEV/TMZ
Albert Lai[2010]	31/40	39/70	2/23	40/40	28/47	RT+TMZ+BV/UCLA/KPLA Control RT/TMZ
B.Chauffert[2014]	26/23	34/37	/	/	/	BEV+IRI/TMZ+RT

Offset risk included in the study

The results of the bias risk assessment included in the study are shown in figure 2.

Meta-analysis results

Progression-free survival

Six studies[10,12-14,18-19] reported median progression-free survival (BEV group, n=1160) and Non-BEV group (n=1027). Results: HR=0.71, 95%CI, 0.65 to 0.79; suggested that the median progression-free survival of gliomas treated with BEV was significantly longer than that of malignant gliomas treated with Non-BEV (P<0.00001), as shown A in figure 3 .

Ten studies[10-19] compared PFS ratios at different follow-up between the Bev group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=71%, P<0.00001), so the random effect model was used. The results showed that the combined OR values of 6 months, 12 months, 18 months, 24 months and 30 months are (3.31, 95%CI 2.74 to 4.00, p<0.00001), (2.05, 95%CI 1.70 to 2.49, p<0.00001), (1.31, 95%CI 1.02 to 1.69, p=0.03), (0.83, 95%CI 0.50 to 1.37, p=0.47), (0.62, 95%CI 0.39 to 0.97, p=0.04).,as shown C in figure 3 .

Overall survival time

Six studies[10,12-14,18-19] reported the median overall survival time, and there was no significant difference in the heterogeneity test (I^2=72%, p=0.54), so the random effect model was used for data analysis. Results: HR=0.93, 95%CI, 0.75 to 1.16, suggesting that there was no significant difference in median overall survival time between the BEV group and Non-BEV group (P=0.54), as shown B in figure 3 .

Six studies[10,12-14,18-19] compared OS ratios at different follow-up between the Bev group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=38%, P<0.03). The Random effect model was used, and the results show that the combined OR values of 6 months,12 months,18 months, 24 months, and 36 months are (4.94, 95%CI 3.60-6.78, P<0.00001), (2.62, 95%CI 1.96-3.49, P<0.00001), (2.06, 95%CI 0.96-4.40, P=0.05), (4.02, 95%CI 2.19-7.36, P<0.00001), (1.73, 95%CI 0.93-3.23, P=0.09), as shown D in figure 3 .

Adverse reaction

As shown in figure 4, there were six studies[10-11,13-15] that compared adverse reactions between the BEV group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=58%, P<0.00001), and the random effect model was used. The results showed the combined OR values of hypertension, hemorrhage, cerebral hemorrhage, albuminuria, and thromboembolism as follows: hypertension (4.94, 95%CI 3.60 to 6.78, P<0.00001), hemorrhage (2.62, 95%CI 1.96 to 3.49, P<0.00001), cerebral hemorrhage (2.06, 95%CI 0.96 to 4.40, P=0.05), proteinuria (4.02, 95%CI 2.19 to 7.36, P<0.00001) and thromboembolism (1.73, 95%CI 0.93 to 3.23, P=0.09).

Sensitivity analysis

The sensitivity test was used to evaluate the stability of OS, PFS, and adverse reactions in the included literature, which showed that all values remained in the confidence interval on both sides after one by one elimination. Hence, it can be concluded that all the included literature is stable, as shown in figures 5 .

Publication bias

As shown in figures 6, except for the adverse reactions and the funnel chart of the median OS with HR, the publication bias of the funnel chart was higher, while the rest of the funnel chart was mainly concentrated at the top. Moreover, the symmetry was also proper, so it was concluded that the possibility of publication bias was small.

DISCUSSION

According to the histopathological and clinical features, gliomas are divided into astrocytoma, oligodendroglioma, and ependymoma, which are the most common malignant tumors derived from neuroepithelium[20]. Although the technical level of surgical intervention, radiotherapy, and chemotherapy[21] in the treatment of glioma has been greatly improved, there is still a high recurrence rate with increased mortality, which necessitates a more effective therapy. Glioma affects the body through a variety of pathophysiological processes, in which angiogenesis plays an important role in the occurrence and development of glioma, hence blocking angiogenesis has become a new direction of treatment. Bevacizumab is an anti-VEGF antibody against vascular endothelial growth factor[22], which acts mainly by competing against the binding of VEGF, to VEGFR on the membrane of target cells. Studies reported by Pope et al.[23] and others have shown that the high levels of VEGF affect blood vessel density and tumor grade. Some studies have shown that Ang2/Tie2[24,25] and STAT3[26] are two important signal pathways in anti-angiogenic therapy, which play a vital role in inhibiting peritumoral edema and thus increase of neurological symptoms. In order to better understand the advantages and disadvantages of BEV on glioma, we performed this meta-analysis study which can enlighten and provide a better understanding of the efficacy and safety of BEV through a systematic review.

The results of our study showed that the PFS of the BEV group was higher than that of the Non-BEV group during the follow-up period of < 18 months, but the PFS of the BEV group was lower than that of the Non-BEV. Moreover, among the BEV group when the follow-up time was 30 months, the OS was higher at 6 months and 12 months, but there was no significant difference between the BEV group and Non-BEV group after 12 months. The study of Li YD[27] showed that the progression-free survival time at 24 months and 36 months in the bevacizumab group was lower than that in the the

non-bevacizumab group. However, the study result from Liao KL[28] showed that the incidence of PFS was higher in newly diagnosed HGG plus BEV, and the combination therapy involving BEV did not improve the OS. The AVAglio[29] trial showed that patients treated with bevacizumab had significant advantages in terms of PFS (6.2months vs 10.6 months) and quality of life maintenance, but did not show an advantage in terms of OS (16.8months vs 16.7 months). Compared with the patients without bevacizumab, 2.2% of patients treated with bevacizumab confirmed pseudo-progression. Meanwhile, 9.3% of patients treated with non-bevacizumab[30] reported that the median PFS of bevacizumab combined with temozolomide and radiotherapy was nearly twice as high as that of 3-14 months in a single phase 2 clinical trial, but there was no significant improvement in overall survival. Chinot *et al.*[31] and Gilbert *et al.*[32] conducted phase 3 clinical trials in the placebo control group, respectively. The results showed that the PFS of the experimental group increased by 40%, 71%, compared with the control group. Brandes[33] *et al.* and Wick[34] also concluded that BEV failed to improve the OS of glioma patients in a randomized study of bevacizumab. BEV can increase the progression-free survival time of patients but cannot significantly improve OS.

Studies have shown that long-term use of BEV does not increase patients' PFS, on the contrary, it may decrease PFS over time, due to the adverse reactions caused by BEV. This study showed five common adverse reactions including hypertension, hemorrhage, cerebral hemorrhage, albuminuria, and thromboembolism upon initiating BEV therapy, but the toxicity of antiangiogenic therapy was generally well tolerated. A phase II trial of Japanese study[35] showed that the most common side effects were albuminuria, hypertension, hemorrhage, fever, and epilepsy. Studies[36] showed that the incidence of adverse reactions above grade 3 was 27.1% to 46.4%. The most common events reported were thromboembolism, hypertension, epilepsy, fatigue, and intestinal perforation. Zhang Li[37] evaluated cases from 20 articles about adverse reactions caused by BEV in 357 patients and found that the main adverse reactions were associated with cardiovascular and hematological diseases. Norden[38] evaluated 64 glioma patients treated with anticoagulants with BEV and those without anticoagulants. The results showed that the rates of intracranial hemorrhage and other bleeding sites in patients treated with anticoagulants were significantly higher than those in patients treated with BEV alone. However, the rate of severe intracranial hemorrhage was within an acceptable range, hence the anticoagulants were recommended for patients with symptomatic venous thrombosis treated with BEV. Therefore, when bevacizumab was used in the clinic, it was necessary to closely observe for any adverse drug reactions, monitor blood pressure, blood coagulation function, and other indexes, and deal with the symptoms in time. We also need more large-scale phase III clinical

studies to prove whether PFS can be improved by improving adverse reactions. Collectively, improving the PFS may enhance great economic and survival benefits to the patients and society, and may further reinforce the successful therapeutic applications of BEV in gliomas.

CONCLUSIONS

The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the higher incidence of adverse events caused by the long-term use of BEV.

Limitations

In this study, the preoperative symptoms and the scope and degree of surgical resection are not taken into account. Hence, a large study in terms of more samples and higher quality clinical parameters may further validate the conclusive evidence.

Declaration:

Contributors WH、FXXandZXP contributed to conception and design. WK、MST and YYF contributed to data acquisition or analysis and interpretation of data. WH、FXX、ZXP、WK、MSTandYYFwere involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing: No additional data are available.

Picture description

In this paper, the pictures are uploaded in a separate form, and the pictures are merged, leaving 6 important and indispensable pictures.

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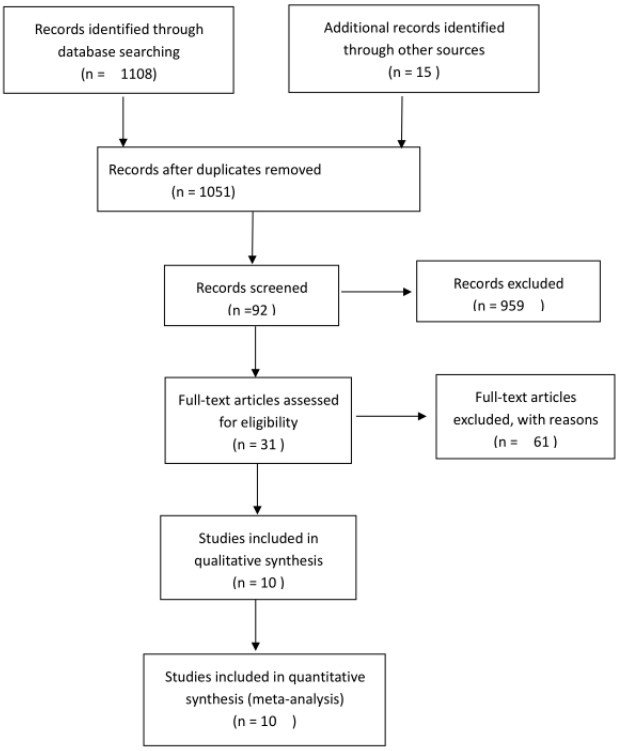

Figure 1: document screening process and results

168x237mm (120 x 120 DPI)

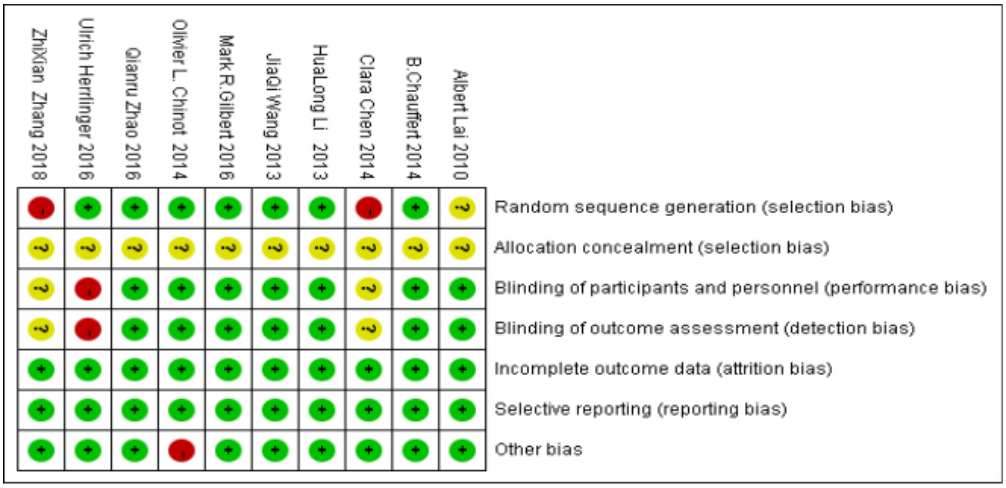

Figure 2: bias risk assessment form

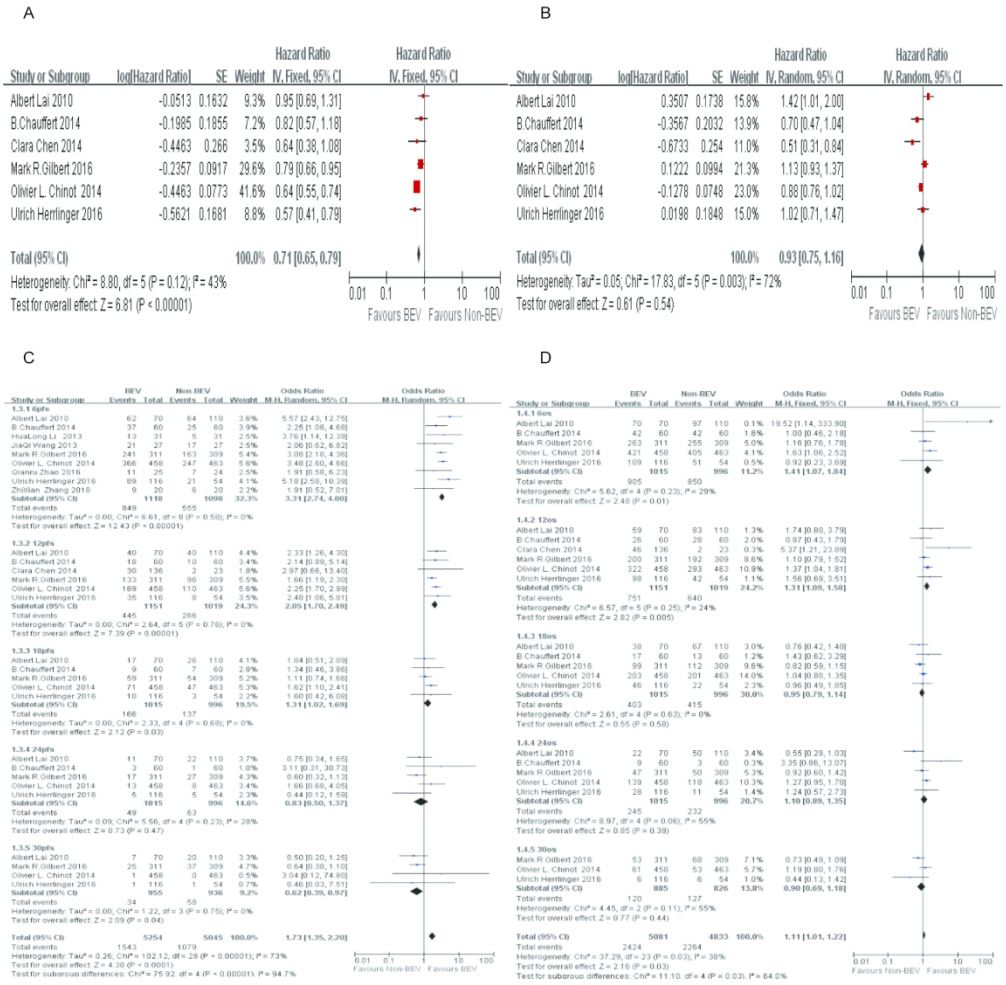

Figure 3 shows:A)HR of median PFS in BEV group and Non-BEV group in the treatment of glioma;B)HR of median OS in BEV group and Non-BEV group in the treatment of glioma;C)OR of PFS at each follow-up time in BEV group and Non-BEV group in the treatment of glioma; D)OR of OS at each follow-up time in the treatment of glioma in the BEV group and Non-BEV group

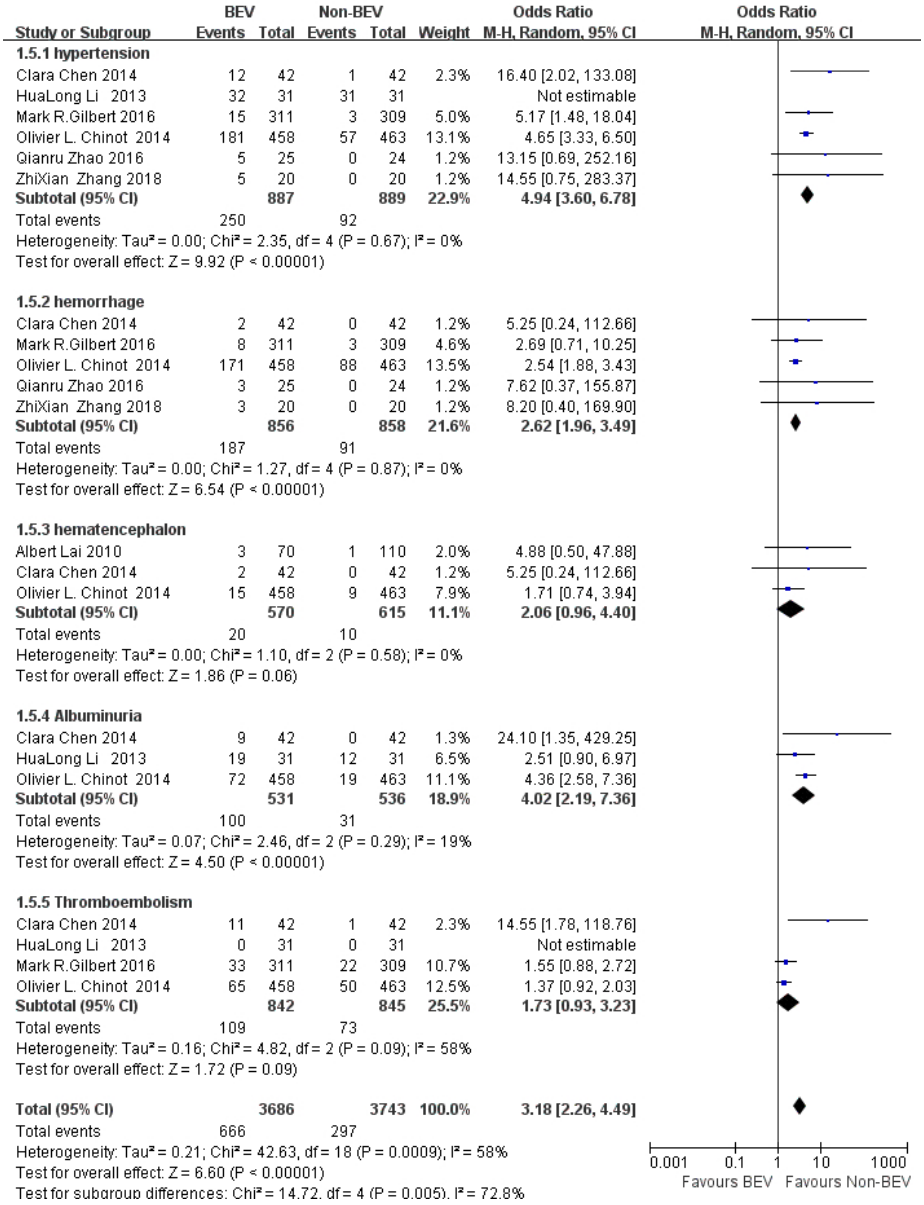

Figure 4: OR of adverse reactions in the treatment of glioma in the BEV group and Non-BEV group

150x196mm (120 x 120 DPI)

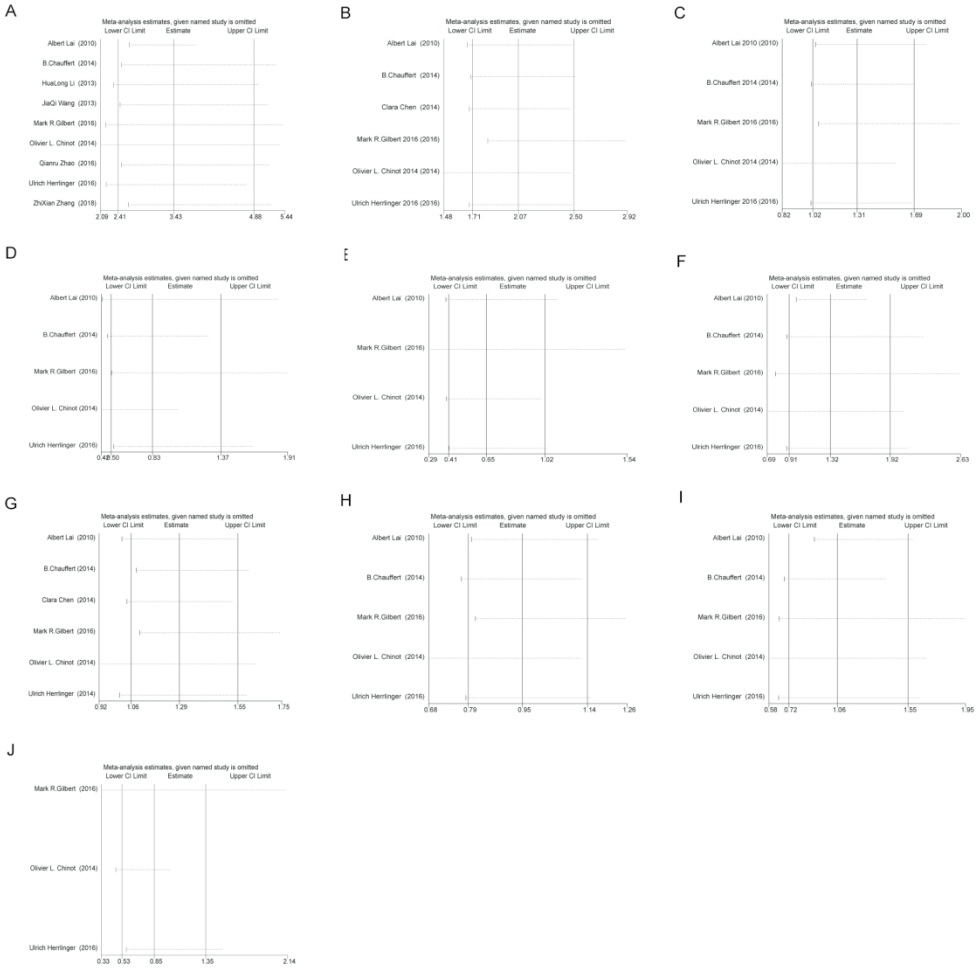

Figure 5 shows:Comparison of the sensitivity analysis offunnel at each follow-up timeA) PFS6 combined with OR; B) PFS12 combined with OR;
C) PFS18 combined with OR;D) PFS24 combined with OR; E) PFS30 combined with OR;F)OS6 combined with OR; G)OS12 combined with OR;H)OS18 combined with OR;I)OS24 combined with OR;J) OS30 combined with OR

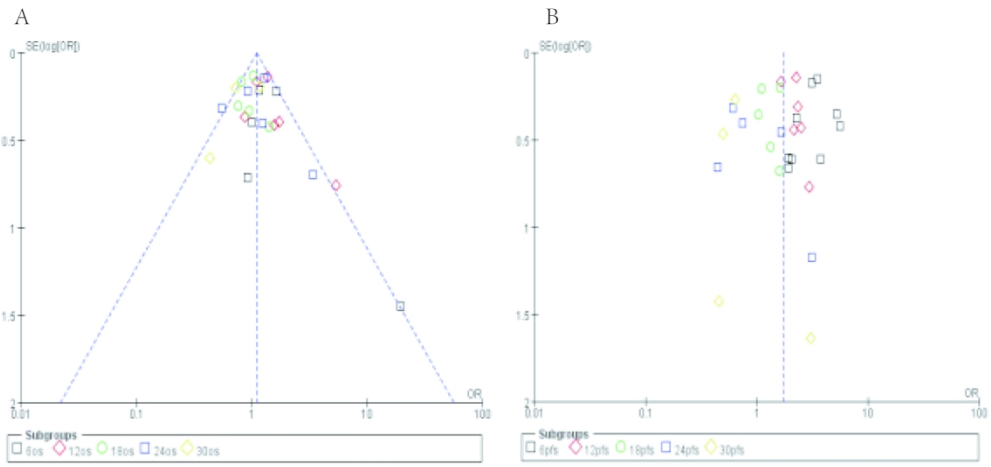

Figure 6 shows:A)The forest map shows:A)OS combined with OR funnel at each follow-up time;B) PFS and OR funnel diagram at each follow-up time

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Systematic review and meta-analysis.	
ABSTRACT			
Structured summary	2	**Objective:** This study evaluated the efficacy and safety of bevacizumab in patients with glioma. **Design:** Systematic review and meta-analysis. **Data sources:** The data were collected using online search criteria from the databases like PubMed, Embase, The Cochrane Library, OVID biomedical database, Chinese periodical full-text database (CNKI), and Chinese biomedical literature service system (CBM) from inception up to April 2020. **Intervention:** Bevacizumab (BEV) and other interventions. **Primary and secondary outcome measures:** The main indicators included progression-free survival rate and overall survival rate, and the secondary indicators were adverse reactions. **Results:** A total of 10 clinical center trials were included in this study for meta-analysis, including 2392 patients . The results of the meta-analysis showed that the median progression-free survival rate of the BEV group (PFS) was significantly higher than that of the Non-BEV group (P<0.00001). When compared with the PFS rate of each stage, the PFS rate of the BEV group was 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03). The PFS of the BEV group was higher than that of Non-BEV group at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47). At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), the PFS of the Non-BEV group was lower than that of the Non-BEV group.Moreover, we have compared overall survival rate and the five common adverse reactions, including hypertension ,hemorrhage , and cerebral hemorrhage , Proteinuria and thromboembolism . **Conclusion:** BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the high incidence of adverse events	

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		caused by long-term use of BEV. More prospective studies are needed to verify it in the future.	
INTRODUCTION			
Rationale	3	Brain glioma (High-Grade Glioma, HGG) is the most common primary intracranial tumor, accounting for about 27% of central nervous system tumors and 80% of intracranial malignant tumors[1]. The median survival time reported with brain glioma is 14-16 months[2]. The Surgical intervention combined with radiotherapy and chemotherapy are often followed for treatment of such cases, but because of its high invasive nature, it often relapses in a short time with poor prognosis. The emergence of temozolomide has considerably delayed the development of glioma to some extent, but the survival rate and quality of life of patients are still very low. Therefore, looking for better drugs to prevent and delay the postoperative recurrence of glioma has become the focus of current research. In recent years, more and more studies have shown that malignant glioma is the tumor with the highest degree of vascularization[3]. The nature of proliferation is characterized by obvious proliferative vascular lumen and with abnormal proliferation of neovascularization which participates in the construction of tumor microenvironment[4]. It is closely related to the growth, invasion, and metastasis of the tumor, and positively correlated with the extent of malignancy and prognosis of the tumor. Recently, the unique biological characteristics of gliomas indicated that angiogenic factors may play an important role in its treatment and have become the focus of research. Humanized anti-vascular endothelial growth factor monoclonal antibody-bevacizumab[5], as a representative drug of anti-angiogenic therapy, was approved for recurrent glioblastoma by FDA in 2009[6] and is listed in China in 2010 by CFDA. According to the radiological response rate, bevacizumab has been approved for recurrent glioblastoma in the United States and many other countries[7,8]. Although bevacizumab (BEV) has become an important part of HGG therapy, the safety and long-term efficacy of BEV are not clear. Therefore, we conducted a clinical meta-analysis to evaluate the safety and adverse reactions of BEV in patients with HGG, in order to provide a reference for clinical application.	
Objectives	4	This study evaluated the efficacy and safety of bevacizumab in patients with glioma.	

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METHODS			
Protocol and registration	5	Not Protocol and registration	
Eligibility criteria	6	(1) Study subjects: the participants were patients of any age, whose histology was confirmed to be HGG. They may have undergone any form of surgery to achieve histological diagnosis (biopsy or resection); (2) Study type: The clinical control study; (3) Intervention: BEV in bevacizumab group must include bevacizumab, which can be used alone or in combination with multiple drugs. The control group (Non-BEV) refers to treatment that does not include anti-angiogenesis, which can be placebo or supportive therapy, or active intervention (such as chemotherapy). (4) Outcome indicators: included in accordance with the following arbitrary outcome indicators:①main indicators: progression-free survival (PFS)rate, defined as the time from randomization to death or disease progression of any cause, and overall survival(OS) rate, defined as the time from randomization to death. ② key indicators: adverse events classified according to the World Health Organization (WHO) or the General terminology Standard of the National Cancer Institute (NCI-CTCAE (CTCAE2017)), including the percentage of treatment-related deaths.	
Information sources	7	We collected all the clinical experimental studies of anti-angiogenic therapy in the treatment of gliomas, retrieved through a database search including PubMed database, Embase database, The Cochrane Library, CBM, Biomedical database, China Journal full-text database (CNKI), Wanfang, from the establishment of the database to April 2020.	
Search	8	The search strategy followed included a combination of subject words and free words, and the retrieval strategy was determined after several pre-searches. The main search words included: "glioma", "angiogenesis inhibitors", "vascular endothelial growth factors", "VEGF", and "clinical study". Additionally, we also manually searched the reference list of all articles on this topic to check and enhance the retrieval of other related publications. All search results are evaluated according to the (PRISMA) statement of "preferred reporting items for systematic review and meta-analysis".	
Study selection	9	Studies were included if they fulfilled the following criteria: The above eligibility criteria. Studies were excluded if they fulfilled the following conditions: Non-clinical control studies, incomplete	

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		abstract information, conference papers, reviews, and case reports. In addition, the literature of repeated publication and incomplete data that cannot extract valid data should also be excluded.	
Data collection process	10	Literature screening, data extraction, and cross-checking were carried out by two independent researchers according to the initial inclusion and exclusion criteria, and if there were any differences, it was discussed or judged with the assistance of a third person, and contact and supplement the missing data with the author as far as possible. During the literature screening, the title and the abstract were read initially, and after excluding the obviously irrelevant literature, the full text was read to determine whether to include it or not. Upon matching the inclusion criteria of requirements	
Data items	11	the following contents were extracted: (1) the basic information, including title, author, published country, publication date, research type; (2) study subjects, including the number of cases in each group, average age; (3) interventional factors, including the specific details of exposure factors, follow-up time, etc.; (4) the outcome indicators.	
Risk of bias in individual studies	12	Using the Cochrane collaboration tool, the risk of bias in individual studies was assessed from seven aspects (sequence generation, allocation hiding, uninformed participants and people, incomplete outcome data, selective reports, and other biases and risks) [9]. Finally, each project was evaluated at three levels: low risk, unclear, and high risk. The two authors conducted independent quality assessments and any differences among them were resolved through discussions with a third research expert.	
Summary measures	13	PFS, OS, and adverse reactions were analyzed by Meta with RevMan5.1 software. The data were counted by risk ratio (hazard ratio; HR) and odds ratio (Odds ratio; OR). The interval estimation was expressed by 95%CI, and the test level of the effect quantity was α = 0.05.	
Synthesis of results	14	The heterogeneity among the included results was analyzed by using the "I^2" (the level is α = 0.1a).Simultaneously, combined with I^2 to quantitatively judge the size of heterogeneity.	

Section/topic	#	Checklist item	Reported on page #

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Risk of bias across studies	15	Publication bias was detected by the funnel chart method.	
Additional analyses	16	Stata15.1 was used for sensitivity analysis, and the method of examining the influence of a single study was used to eliminate them one by one. The consistency of the results obtained after the above transformation shows that the results of Meta-analysis were stable, otherwise, they were regarded as unstable.	
RESULTS			
Study selection	17	A total of 1108 related literature were obtained in the initial examination. After screening the literature one by one, a total of 1123 patients were included in 10 clinical studies[10-19]. The database and the number of documents retrieved are as follows: PubMed (nasty 259), The Cochrane Library (nasty 153), EMbase (nasty 155), CNKI (nasty 118), CBM (nasty 358), WangFang (nasty 65). The flow chart and the results of literature retrieval are shown in figure 1.	
Study characteristics	18	**The basic characteristics of the inclusion study** For the inclusion study, the basic information for inclusion is completed using pre-developed forms (Tables 1, 2). **Offset risk included in the study** The results of the bias risk assessment included in the study are shown in figure 2.	
Risk of bias within studies	19	**Publication bias** As shown in figures 6 (see appendix), except for the adverse reactions and the funnel chart of the median OS with HR, the publication bias of the funnel chart was higher, while the rest of the funnel chart was mainly concentrated at the top. Moreover, the symmetry was also proper, so it was concluded that the possibility of publication bias was small.	

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Results of individual studies	20	**Progression-free survival** Six studies[10,12-14,18-19] reported median progression-free survival (BEV group, n=1160) and Non-BEV group (n=1027). Results: HR=0.71, 95%CI, 0.65 to 0.79; suggested that the median progression-free survival of gliomas treated with BEV was significantly longer than that of malignant gliomas treated with Non-BEV (P<0.00001), as shown A in figure 3 . **Overall survival time** Six studies[10,12-14,18-19] reported the median overall survival time, and there was no significant difference in the heterogeneity test (I^2=72%, p=0.54), so the random effect model was used for data analysis. Results: HR=0.93, 95%CI, 0.75 to 1.16, suggesting that there was no significant difference in median overall survival time between the BEV group and Non-BEV group (P=0.54), as shown B in figure 3 . **Adverse reaction** The results showed the combined OR values of hypertension, hemorrhage, cerebral hemorrhage, albuminuria, and thromboembolism as follows: hypertension (4.94, 95%CI 3.60 to 6.78, P<0.00001), hemorrhage (2.62, 95%CI 1.96 to 3.49, P<0.00001), cerebral hemorrhage (2.06, 95%CI 0.96 to 4.40, P=0.05), proteinuria (4.02, 95%CI 2.19 to 7.36, P<0.00001) and thromboembolism (1.73, 95%CI 0.93 to 3.23, P=0.09).	
Synthesis of results	21	**Progression-free survival** Ten studies[10-19] compared PFS ratios at different follow-up between the Bev group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=71%, P<0.00001), so the random effect model was used. The results showed that the combined OR values of 6 months, 12 months, 18 months, 24 months and 30 months are (3.31, 95%CI 2.74 to 4.00, p<0.00001), (2.05, 95%CI 1.70 to 2.49, p<0.00001), (1.31, 95%CI 1.02 to 1.69, p=0.03), (0.83, 95%CI 0.50 to 1.37, p=0.47), (0.62, 95%CI 0.39 to 0.97, p=0.04).,as shown C in figure 3 . **Overall survival time**	

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		Six studies[10,12-14,18-19] compared OS ratios at different follow-up between the Bev group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=38%, P<0.03). The Random effect model was used, and the results show that the combined OR values of 6 months,12 months,18 months, 24 months, and 36 months are (4.94, 95%CI 3.60-6.78, P<0.00001), (2.62, 95%CI 1.96-3.49, P<0.00001), (2.06, 95%CI 0.96-4.40, P=0.05), (4.02, 95%CI 2.19-7.36, P<0.00001), (1.73, 95%CI 0.93-3.23, P=0.09), as shown D in figure 3 . **Adverse reaction** As shown in figure 4, there were six studies[10-11,13-15] that compared adverse reactions between the BEV group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=58%, P<0.00001), and the random effect model was used.	
Risk of bias across studies	22	As shown in figures 6 (see appendix), except for the adverse reactions and the funnel chart of the median OS with HR, the publication bias of the funnel chart was higher, while the rest of the funnel chart was mainly concentrated at the top. Moreover, the symmetry was also proper, so it was concluded that the possibility of publication bias was small.	
Additional analysis	23	The sensitivity test was used to evaluate the stability of OS, PFS, and adverse reactions in the included literature, which showed that all values remained in the confidence interval on both sides after one by one elimination. Hence, it can be concluded that all the included literature is stable, as shown in figures 5 .	
DISCUSSION			
Summary of evidence	24	Studies have shown that long-term use of BEV does not increase patients' PFS, on the contrary, it may decrease PFS over time, due to the adverse reactions caused by BEV. This study showed five common adverse reactions including hypertension, hemorrhage, cerebral hemorrhage, albuminuria, and thromboembolism upon initiating BEV therapy, but the toxicity of antiangiogenic therapy was generally well tolerated. A phase II trial of Japanese study[35] showed that the most common side effects were albuminuria, hypertension, hemorrhage, fever, and epilepsy. Studies[36] showed that the incidence of adverse reactions above grade 3 was 27.1% to 46.4%. The most common events reported were thromboembolism,	

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		hypertension, epilepsy, fatigue, and intestinal perforation. Zhang Li[37] evaluated cases from 20 articles about adverse reactions caused by BEV in 357 patients and found that the main adverse reactions were associated with cardiovascular and hematological diseases. Norden[38] evaluated 64 glioma patients treated with anticoagulants with BEV and those without anticoagulants. The results showed that the rates of intracranial hemorrhage and other bleeding sites in patients treated with anticoagulants were significantly higher than those in patients treated with BEV alone. However, the rate of severe intracranial hemorrhage was within an acceptable range, hence the anticoagulants were recommended for patients with symptomatic venous thrombosis treated with BEV. Therefore, when bevacizumab was used in the clinic, it was necessary to closely observe for any adverse drug reactions, monitor blood pressure, blood coagulation function, and other indexes, and deal with the symptoms in time. We also need more large-scale phase III clinical studies to prove whether PFS can be improved by improving adverse reactions. Collectively, improving the PFS may enhance great economic and survival benefits to the patients and society, and may further reinforce the successful therapeutic applications of BEV in gliomas.	
Limitations	25	In this study, the preoperative symptoms and the scope and degree of surgical resection are not taken into account. Hence, a large study in terms of more samples and higher quality clinical parameters may further validate the conclusive evidence.	
Conclusions	26	The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the higher incidence of adverse events caused by the long-term use of BEV. In this study, the preoperative symptoms and the scope and degree of surgical resection are not taken into account. Hence, a large study in terms of more samples and higher quality clinical parameters may further validate the conclusive evidence.	
FUNDING			
Funding	27	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors	

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From: 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

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Efficacy and safety of bevacizumab in the treatment of adult gliomas:a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048975.R1
Article Type:	Original research
Date Submitted by the Author:	26-May-2021
Complete List of Authors:	Wang, huan; Xi'an Jiaotong University Medical College First Affiliated Hospital, Fan, Xiaoxuan; Shaanxi University of Chinese Medicine, The First Affiliated Hospital Zhao, Xiaoping; Shaanxi University of Chinese Medicine, The First Affiliated Hospital wang, kai; Shaanxi University of Chinese Medicine Ma, Sitian; Shaanxi University of Chinese Medicine Yang, Yongfeng; Shaanxi University of Chinese Medicine
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Patient-centred medicine
Keywords:	NEUROSURGERY, ONCOLOGY, Head & neck tumours < ONCOLOGY

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Efficacy and safety of bevacizumab in the treatment of adult gliomas:a systematic review and meta-analysis

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Keywords ： glioma,Bevacizumab,efficacy,safety,progression-free survival

Number of words:3833

ABSTRACT

Objective To assess the efficacy and safety of bevacizumab in patients with glioma.

Design Systematic review and meta-analysis.

Participants Adults aged 18 years and above, whose histology was confirmed to be malignant glioma.

Intervention: Bevacizumab and other interventions.

Primary and secondary outcome measures: The main indicators included progression-free survival rate and overall survival rate, and the secondary indicators were adverse reactions.

Results: A total of 10 clinical center trials were included in this study for meta-analysis, including 2392 patients . The results of the meta-analysis showed that the median progression-free survival(PFS) rate of the BEV group was significantly higher than that of the Non-BEV group (P<0.00001). When compared with the PFS rate of each stage,it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03).But at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47)，there was no significant difference between the two groups.At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), the PFS of the BEV group was lower than that of the Non-BEV group.Moreover, The results showed that BEV had no significant effect on improving OS, but the adverse reaction in BEV group was significantly higher than that in non-BEV group.

Conclusion: The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the subgroup of patients, the change of recurrence mode, the optimal dose of drug, the increase of hypoxia, the enhancement of invasiveness and so on.Therefore, it is necessary to carry out more samples and higher quality large-scale research in the future.

Strengths and Limitations of this study

1. We used the Cochrane criteria to assess the risk of bias.
2. The heterogeneity was explored by sensitivity, sub-group.
3. the quality of included studies was largely mod-erate to high.
4. The preoperative symptoms and the scope and degree of surgical resection are not taken into account.

INTRODUCTION

Brain glioma is the most common primary intracranial tumor, accounting for about 27% of central nervous system tumors and 80% of intracranial malignant tumors[1]. The median survival time reported with brain glioma is 14-16 months[2]. The Surgical intervention combined with radiotherapy and chemotherapy are often followed for treatment of such cases, but because of its high invasive nature, it often relapses in a short time with poor prognosis. The emergence of temozolomide has considerably delayed the development of glioma to some extent, but the survival rate and quality of life of patients are still very low. Therefore, looking for better drugs to prevent and delay the postoperative recurrence of glioma has become the focus of current research. In recent years, more and more studies have shown that malignant glioma is the tumor with the highest degree of vascularization[3]. The nature of proliferation is characterized by obvious proliferative vascular lumen and with abnormal proliferation of neovascularization which participates in the construction of tumor microenvironment[4]. It is closely related to the growth, invasion, and metastasis of the tumor, and positively correlated with the extent of malignancy and prognosis of the tumor. Recently, the unique biological characteristics of gliomas indicated that angiogenic factors may play an important role in its treatment and have become the focus of research.

Humanized anti-vascular endothelial growth factor monoclonal antibody-bevacizumab[5], as a representative drug of anti-angiogenic therapy, was approved for recurrent glioblastoma by FDA in 2009[6] and is listed in China in 2010 by CFDA. According to the radiological response rate, bevacizumab has been approved for recurrent glioblastoma in the United States and many other countries[7,8]. Although bevacizumab (BEV) has become an important part of HGG therapy, the safety and long-term efficacy of BEV are not clear. Therefore, we conducted a clinical meta-analysis to evaluate the safety and adverse reactions of BEV in patients with HGG, in order to provide a reference for clinical application.

METHODS

This study was mainly based on the literature research, hence there is no need for ethical identification.

Search strategy

We collected all the clinical experimental studies of anti-angiogenic therapy in the treatment of gliomas, retrieved through a database search includingPubMed, Embase, The Cochrane Library, WanFang, Chinese periodical full-text database (CNKI), and Chinese biomedical literature service system (CBM), from the establishment of the database to April 2020. The search strategy followed included a combination of subject words and free words, and the retrieval strategy was determined after several pre-searches. The main search words included: "glioma", "angiogenesis inhibitors", "vascular endothelial growth factors", "VEGF", and "clinical study". Additionally, we also manually searched the reference list of all articles on this topic to check and enhance the retrieval of other related publications. All search results are evaluated according to the (PRISMA) statement of "preferred reporting items for systematic review and meta-analysis".

Selection criteria

Studies were included if they fulfilled the following criteria: (1) Study subjects: the participants were adults aged 18 years and above, whose histology was confirmed to be malignant glioma. They may have undergone any form of surgery to achieve histological diagnosis (biopsy or resection); (2) Study type: The clinical control study; (3) Intervention: BEV in bevacizumab group must include bevacizumab, which can be used alone or in combination with multiple drugs. The control group (Non-BEV) refers to treatment that does not include anti-angiogenesis, which can be placebo or supportive therapy, or active intervention (such as chemotherapy). (4) Outcome indicators: included in accordance with the following arbitrary outcome indicators: ① main indicators: progression-free survival rate, defined as the time from randomization to death or disease progression of any cause, and overall survival rate, defined as the time from randomization to death. ② key indicators: adverse events classified according to the World Health Organization (WHO) or the General terminology Standard of the National Cancer Institute (NCI-CTCAE (CTCAE2017)), including the percentage of treatment-related deaths.

Studies were excluded if they fulfilled the following conditions: Non-clinical control studies, incomplete abstract information, conference papers, reviews, and case reports. In addition, the literature of repeated publication and incomplete data that cannot extract valid data should also be excluded.

Data extraction

Literature screening, data extraction, and cross-checking were carried out by two independent researchers according to the initial inclusion and exclusion criteria, and if there were any differences, it was discussed or judged with the assistance of a third person, and contact and supplement the missing data with the author as far as possible. During the literature screening, the title and the abstract were read initially, and after excluding the obviously irrelevant literature, the full text was read to determine whether to include it or not. Upon matching the inclusion criteria of requirements, the following contents were extracted: (1) the basic information, including title, author, published country, publication date, research type; (2) study subjects, including the number of cases in each group, average age; (3) interventional factors, including the specific details of exposure factors, follow-up time, etc.; and (4) the outcome indicators.

Quality assessment

Using the Cochrane collaboration tool, the risk of bias in individual studies was assessed from seven aspects (sequence generation, allocation hiding, uninformed participants and people, incomplete outcome data, selective reports, and other biases and risks) [9]. Finally, each project was evaluated at three levels: low risk, unclear, and high risk. The two authors conducted independent quality assessments and any differences among them were resolved through discussions with a third research expert.

Statistical analysis

Analysis of outcome index

PFS, OS, and adverse reactions were analyzed by Meta with RevMan5.1 software. The dichotomy data is expressed as the combined risk ratio (RR) or risk ratio (hazard ratio; HR),The measurement data is expressed as the mean difference (WMD).The interval estimation was expressed by 95%CI, and the test level of the effect quantity was $\alpha = 0.05$.The test for heterogeneity used I^2 statistics.If there is no significant heterogeneity among studies ($I^2 \leq 50\%$), we used the fixed effects model for data consolidation.While there is significant heheterogeneity($I^2 > 50\%$) between the results of the study, the random effects model for data analysis would be used.

Sensitivity analysis

Simultaneously, stata15.1 was used for sensitivity analysis,adopt the method of examining the impact of individual studies and eliminate them one by one, if the

value obtained is within the confidence interval on both sides, the result is stable.otherwise, they were regarded as unstable. Studies included in literature > 10 were used to detect publication bias by funnel chart.

RESULT

Literature screening

A total of 1108 related literature were obtained in the initial examination. After screening the literature one by one, a total of 1123 patients were included in 10 clinical studies[10-19].The flow chart and the results of literature retrieval are shown in figure 1.

The basic characteristics of the inclusion study

For the inclusion study, the basic information for inclusion is completed using pre-developed forms (Tables 1, 2).

Table 1: basic information for inclusion in the study

Study	State	Research type	Cases (experimental/ control)	Ages(experimental / control)	Follow-up time	Outcom
Olivier L. Chinot, M.D[2014[10]]	France	RCT	458/463	20–84/18–79	The last patient was hospitalized for 17 months.	1and2year survival rates、safety and quality of life、PFS、OS
Qianru Zhao[2016[11]]	China	RCT	25/24	24–71/27–	The median follow-up time was 7.9 months	disease control rate、median survival time、OS、PFS
Ulrich Herrlinger[2016[12]]	Germany	RCT	116/54	25–78/26–78	Long-term follow-up until death	PFS–6、PFS、OS

Mark R.Gilbert 2016[13]	Germany	RCT	320/317	>18	6 cycles	OS、PFS
Clara Chen 2014[14]	America	Non-RCT	57/79/23	30–77/24–82/19-78	>1year	OS、PFS
Hualong Li 2020[15]	China	RCT	31/31	18-70/19-69	4 months	PFS6、DCR、Adverse reaction
Zhixian Zhang 2018[16]	China	RCT	20/20	24-74	5.2-18months	PFS6、OS12
Jiaqi Wang2013[17]	China	RCT	27/27	53.6±9.7/54.7±8.8	6months-2years	RR、DCR、Adverse reaction
Albert Lai2010[18]	America	RCT	70/110	31.3-75.8/20.5-90	>42months	OS、PFS、Adverse reaction
B.Chauffert2014[19]	Britain	RCT	60/60	43-69/43-71	6 months	OS、PFS、Adverse reaction

Table 2: basic characteristics of the inclusion study

Study	Male	Female	Open biopsy	Partial resectio	Complete resection	experimental/control
Olivier L. Chinot, M.D2014	282（61.6）/298（64.4）	176（38.4）/165（35.6）	60（13.1）/44（9.5）	210（45.9）/223（48.2）	188（41.0）/196（42.3）	Bevacizumab+RT-TMZ/Placebo+RT-TMZ

Qianru Zhao[2016]	14/12	11/12	/	15/16	10/8	BEV+TMZ/TMZ
Ulrich Herrlinger[2016]	80(69.0) /34(63.0)	36(31.0) /20(37.0)	0/2(3.7)	58(50.0)/27(50.0)	58 (50.0)/25 (46.3)	BEV+IRI/TMZ
Mark R.Gilbert 2016	/	/	/	/	/	Bevacizumab/ Placebo
Clara Chen 2014	30(53)/45(57)/15(65)	57/79/23 27(47)/34(43)/8(35)	34(60)/44(56)/14(61)	20(35)/33(42)/9(39)	3(5)/2(2))/0(0)	Bevacizumab monotherapy /Bevacizumab combination /Nonbevacizumab
Hualong Li[2020]	19/18	12/13	/	/	/	TMZ+BEV/TMZ
Zhixian Zhang 2018	22	18	/	18	22	BEV+TMZ/ Gamma knife +TMZ/
Jiaqi Wang[2013]	16/14	11/13	/	/	/	TMZ+BEV/TMZ
Albert Lai[2010]	31/40	39/70	2/23	40/40	28/47	RT+TMZ+BV/UCLA/KPLA Control RT/TMZ
B.Chauffert[2014]	26/23	34/37	/	/	/	BEV+IRI/TMZ+RT

Risk of bias assessment

The results of the bias risk assessment included in the study are shown in figure 2.

Meta-analysis results

Progression-free survival

Six studies[10,12-14,18-19] reported median progression-free survival (BEV group, n=1160) and Non-BEV group (n=1027).There was no significant difference in the heterogeneity test (I^2=43%<50%), so the fixed effect model was used for data analysis.Results suggested that the median progression-free survival of gliomas treated with BEV was significantly longer than that of malignant gliomas treated with Non-BEV (HR=0.71, 95%CI, 0.65 to 0.79,P<0.00001), As shown in figure 3.

Ten studies[10-19] compared PFS ratios at different follow-up between the Bev group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=71%>50%), so the random effect model was used. Through the results found it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03).But at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47), P > 0.05, so there was no significant statistical difference between the two groups.At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), 0.61 < 1, the diamond pattern falls on the group that supports Non-BEV group,so the PFS of the BEV group was lower than that of the Non-BEV group.as shown in figure 4.

Overall survival time

Six studies[10,12-14,18-19] reported the median overall survival time, and there was a significant difference in the total heterogeneity test (I^2=72%>50%)，so the random effect model was used. Results suggesting that there was no significant difference in median overall survival time between the BEV group and Non-BEV group (HR=0.93, 95%CI, 0.75 to 1.16,P=0.54), as shown in figure 5.

Six studies[10,12-14,18-19] compared OS ratios at different follow-up between the Bev group and the Non-BEV group. there was no significant difference in the heterogeneity test (I^2=38%<50%), so the fixed effect model was used for data analysis. Through the results found it was found that the OS in the BEV group was higher than that in the Non-BEV group at 6 months(1.41； 95%CI， 1.07-1.84； P=0.01),12 months(1.31；95%CI，1.09-1.58；P=0.005).But at18 months （0.95； 95%CI，0.79-1.14；P=0.58）, 24 months（1.10；95%CI，0.89-1.35；P=0.39）, and 30 months（0.90； 95%CI， 0.69-1.18； P=0.44), P > 0.05, so there was no significant statistical difference between the two groups,as shown in figure 6.

Adverse reaction

As shown in figure7, there were six studies[10-11,13-15] that compared adverse reactions between the BEV group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=58%>50%), and the random effect model was used. The results showed the combined OR values of hypertension, hemorrhage, cerebral hemorrhage, albuminuria, and thromboembolism as follows: hypertension (4.94, 95%CI 3.60 to 6.78, P<0.00001), hemorrhage (2.62, 95%CI 1.96 to 3.49, P<0.00001), cerebral hemorrhage (2.06, 95%CI 0.96 to 4.40, P=0.05), proteinuria (4.02, 95%CI 2.19 to 7.36, P<0.00001) and thromboembolism (1.73, 95%CI 0.93 to 3.23, P=0.09).Through the results found it was found that the adverse reactions in the BEV group was higher than that in the Non-BEV group .

Sensitivity analysis

The sensitivity test was used to evaluate the stability of OS, PFS, and adverse reactions in the included literature, which showed that all values remained in the confidence interval on both sides after one by one elimination. Hence, it can be concluded that all the included literature is stable, as shown in figures 8,9.

Publication bias

As shown in figures 10, the funnel chart was mainly concentrated at the top. Moreover, the symmetry was also proper, so it was concluded that the possibility of publication bias was small.

DISCUSSION

According to histopathological and clinical features, gliomas are divided into astrocytoma, oligodendroglioma, oligodendroglioma and ependymoma, which are the most common malignant tumors derived from neuroepithelium. Although the technical level of surgery, radiotherapy and chemotherapy[20] in the treatment of glioma has been greatly improved, but the recurrence rate and mortality rate are still high，so there is an urgent need for a new treatment. Glioma affects the body through a variety of pathophysiological processes, in which angiogenesis plays an important role in the occurrence and development of glioma, so blocking angiogenesis has become a new direction of treatment. Bevacizumab is an anti-(VEGF) antibody against vascular endothelial growth factor[21], which acts mainly by competing against VEGF, and binding to VEGFR on the target cell membrane. Pope[22] and other studies have shown that the high surface of VEGF affects blood vessel density and tumor grade. Some studies have shown that Ang2/Tie2[23,24] and STAT3[25] are two important signal pathways in anti-angiogenic therapy, which play a good role in inhibiting peritumoral edema and the increase of neurological symptoms. In order to better understand the advantages and

disadvantages of BEV on glioma, this study has a better understanding of the efficacy and safety of BEV through systematic review.

The results of our study showed that the PFS of BEV group was higher than that of Non-BEV group during the follow-up period of < 18 months, but when the follow-up time was 30 months， the PFS of BEV group was lower than that of Non-BEV;meanwhile，It was found that the OS in the BEV group was higher than that in the Non-BEV group at 6 months,12 months，but after 12 months, there was no statistically significant difference between the BEV group and the non-BEV group.The study of Li YD[26] showed that the progression-free survival time at 24 months and 36 months in the bevacizumab group was lower than that in the non-bevacizumab group;The results of LiaoKL[27] showed that a higher incidence of PFS could be obtained by adding BEV to newly diagnosed GB, and this combined treatment did not improve OS.The AVAglio[28] trial showed that patients treated with bevacizumab had significant advantages in PFS (6.2 months vs. 10.6 months) and maintenance of life quality, but showed no advantages in OS (16.8 months vs. 16.7 months).2.2% of patients treated with bevacizumab confirmed false progression, compared with 9.3% of patients treated with non-bevacizumab.Vredenburgh[29] found in a single-group clinical phase 2 experimental study that the median PFS of bevacizumab combined with temozolomide and radiotherapy reached nearly twice the standard of 3-14 months,however the overall survival was not significant Improvement.Chinot[30] and Gilbert[31] conducted phase 3 clinical trials with a placebo control group,the results showed that PFS increased by 40%-71% compared with the control group. Special related research on OS, Brandes[32] and Wick[33] also found that BEV failed to improve OS of patients with glioma in a randomized study analyzing bevacizumab.From the above research,BEV can improve the PFS of glioma patients within 18 months,but the PFS of patients may be reduced after 30 months.It has no obvious significance to improve OS.

This study showed that after the application of BEV, there were five common adverse reactions: hypertension, hemorrhage, cerebral hemorrhage, albuminuria and thromboembolism.A phase II trial of Japanese[34] showed that the most common side effects were albuminuria, hypertension, hemorrhage, fever and epilepsy. Studies[35] showed that the incidence of adverse reactions above grade 3 was 27.1% to 46.4%,the most common events were thromboembolism, hypertension, epilepsy, fatigue and intestinal perforation. Zhang Li[36] searched 20 articles about adverse reactions caused by BEV, and found that the main adverse reactions were cardiovascular and hematological diseases. Norden[37] evaluated 64 glioma patients who received BEV anticoagulant therapy and 64 glioma patients who did not

receive anticoagulant therapy,The results showed that the incidence of intracranial hemorrhage and other bleeding in patients treated with anticoagulants was significantly higher than that in patients with BEV alone, but the incidence of severe intracranial hemorrhage was within an acceptable range.Therefore, when using bevacizumab clinically, it is necessary to closely observe drug adverse reactions, monitor blood pressure, coagulation function and other indicators, and deal with symptoms in time.

From the above research results, it can be concluded that long-term use of BEV does not increase the patient's PFS, BEV can improve the PFS of glioma patients within 18 months,but the PFS of patients may be reduced after 30 months. Nagham Kaka found[38] that BEV could have a role in the treatment of particular subgroups of patients with newly diagnosed GBM.Several studies[39,40] have found that the median PFS of patients with methylation is longer than that of MGMT unmethylated tumors treated with RT and TMZ combined with BEV.Sandmann and colleagues[41] found that BEV combined with standard TMZ and RT can improve the survival rate of neurotumors, while poorly differentiated mesenchymal tumors may make tumors resistant to BEV over time. Adilijiang and Colleagues[42] found that treatment with BEV and TMZ results in the upregulation of certain microenvironment related genes in IDH1 mutant tumors in vitro, specifically those involving immune response and extracellular matrix organization.Therefore, The question of whether the limitation of BEV in the treatment of gliomas is due to fixed subsets deserves constant attention.

Studies have shown[43,44] that antiangiogenic therapy can lead to a transition of glioma to a more aggressive phenotype.In retrospective analysis[45,46] a trend toward enhanced infiltra-tive disease was seen in bevacizumab-treated glioma patients suggesting that enhanced tumor inhibition may be a conse-quence of VEGF signaling blockade.Shiao-Pei Weathers[47] shows that determining the best biological dose and the subgroup of patients most likely to obtain long-lasting benefits can improve the durability of bevacizumab.Victor A Levin[48] found treatment for recurrent GBM with BEV appears to improve survival at a dose lower than that in the FDA drug insert. Study[49] suggest that the higher dosage of BEV utilized may have impacted survival benefits.Animal models[50] also suggest that higher dose of anti-VEGF treatment, resulting in more hypoxia, may increase tumor aggressiveness.Ryota Tamura[51] found that high doses and long-term use of anti-VEGF/VEGFR may lead to hypoxia.Shiao-Pei Weathers[47] proposed in tumors where excessive vascular pruning takes place, hypoxia exacerbated by antiangiogenic therapy is likely responsible for initiating a cascade of events. As

mentioned above, there are many possible reasons for the limited efficacy of antiangiogenic therapy.But The lack of a long-lasting response to current antiangiogenic treatment underscores the need for a better understanding of how to use antiangiogenic therapy to optimize radiation and chemotherapy treatments.

CONCLUSIONS

The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the subgroup of patients, the change of recurrence mode, the optimal dose of drug, the increase of hypoxia, the enhancement of invasiveness and so on.BEV treatment has no obvious meaning in improving OS, and it has some side effects, which are acceptable, but we still need to pay close attention to it and take active measures to reduce the side effects.Therefore, it is necessary to carry out more samples and higher quality large-scale research in the future.

Declaration:

Contributors WH、FXXandZXP contributed to conception and design. WK、MST and YYF contributed to data acquisition or analysis and interpretation of data. WH、FXX、ZXP、WK、MSTandYYFwere involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Funding This work was supported by Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, reward/grant number is 2020-ZXY-007.

Ethics Approval This study belongs to data research and is not applicable to ethical review.

Competing interests None declared.

Patient and PublicInvolvement No patient involved.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing All data relevant to the study are included in the article or uploaded as supplementary information.

All the illustrations are as follows:

Figure 1: document screening process and results

PubMed (n=259), The Cochrane Library (n=153), EMbase (n=155), CNKI (n=118), CBM (n=358), WanFang (n=65).

Figure 2: bias risk assessment form

Figur 3:HR of median PFS in BEV group and Non-BEV group in the treatment of glioma

Figur 4:OR of PFS at each follow-up time in BEV group and Non-BEV group in the treatment of glioma

Figure 5:HR of median OS in BEV group and Non-BEV group in the treatment of glioma

Figure 6: OR of OS at each follow-up time in the treatment of glioma in the BEV group and Non-BEV group

Figure 7: OR of adverse reactions in the treatment of glioma in the BEV group and Non-BEV group

Figure 8:A: the sensitivity analysis of PFS6 ;B: the sensitivity analysis of PFS12; C:the sensitivity analysis of PFS18;D:the sensitivity analysis of PFS24;E:the sensitivity analysis of PFS30

Figure 9:A: the sensitivity analysis of OS6 ;B: the sensitivity analysis of OS12; C:the sensitivity analysis of OS18;D:the sensitivity analysis of OS24;E:the sensitivity analysis of OS30

Figure 10:A: funnel chart of PFS at each follow-up time;B: funnel chart of OS at each follow-up time

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51 Ryota Tamura,Toshihide Tanaka,Yasuharu Akasaki,et al.The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications..Med Oncol 2019;37:2.

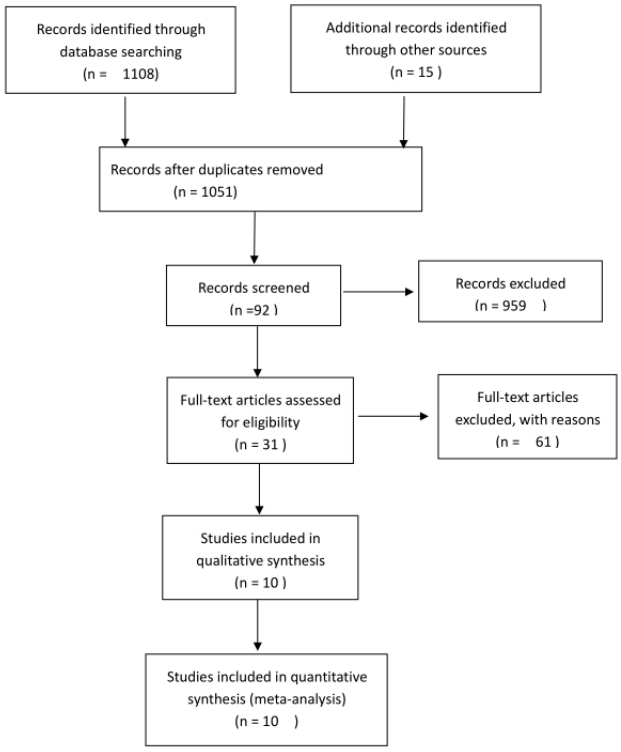


Figure 1: document screening process and results
PubMed (n=259), The Cochrane Library (n=153), EMbase (n=155), CNKI (n=118), CBM (n=358), WanFang (n=65).

168x237mm (120 x 120 DPI)

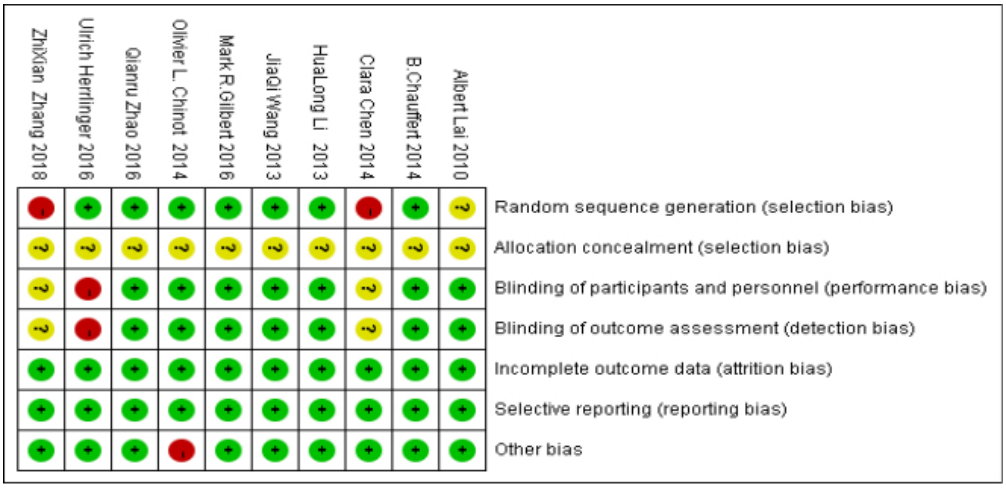
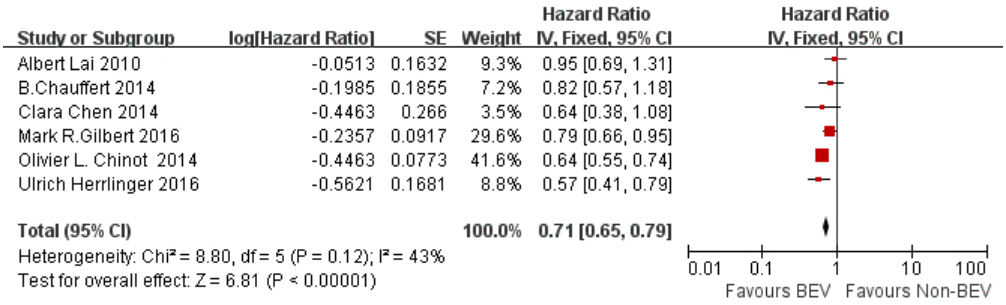
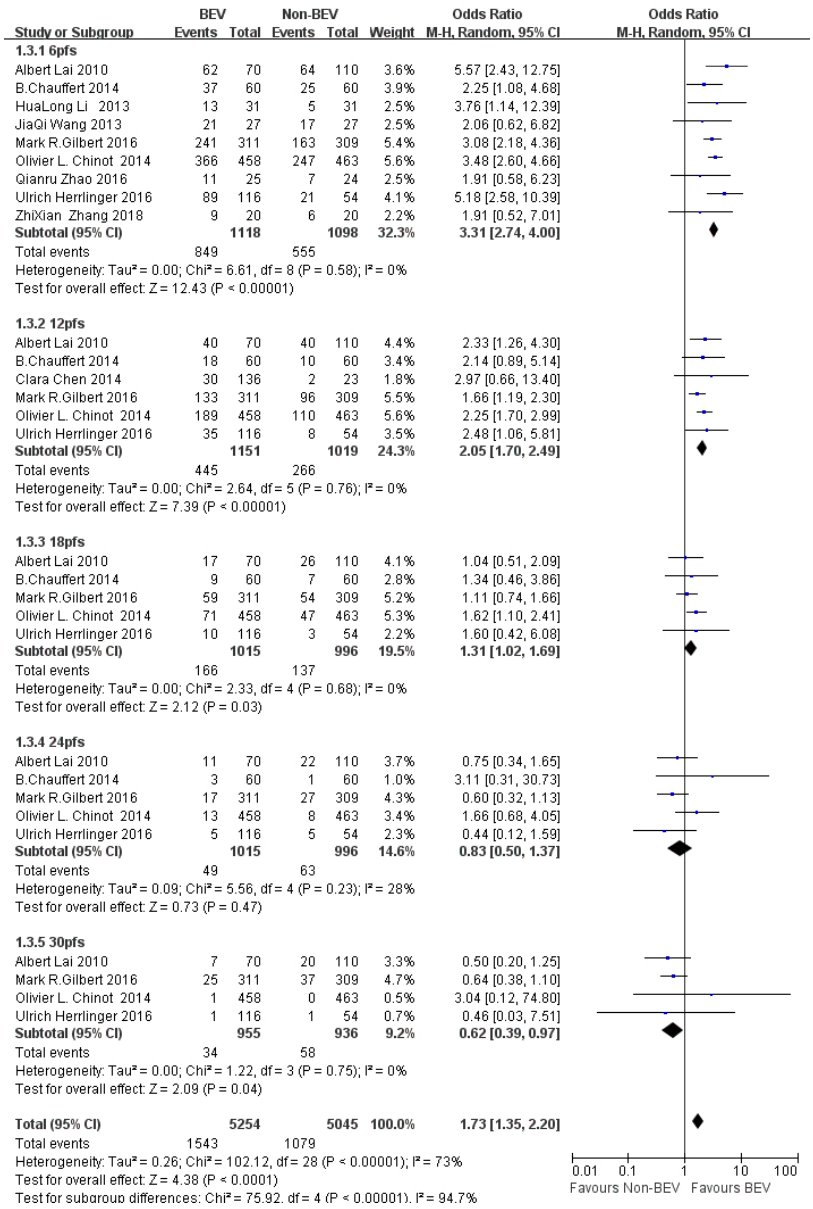


Figure 2: bias risk assessment form



Figur 3:HR of median PFS in BEV group and Non-BEV group in the treatment of glioma

140x44mm (120 x 120 DPI)



Figur 4:OR of PFS at each follow-up time in BEV group and Non-BEV group in the treatment of glioma

150x223mm (120 x 120 DPI)

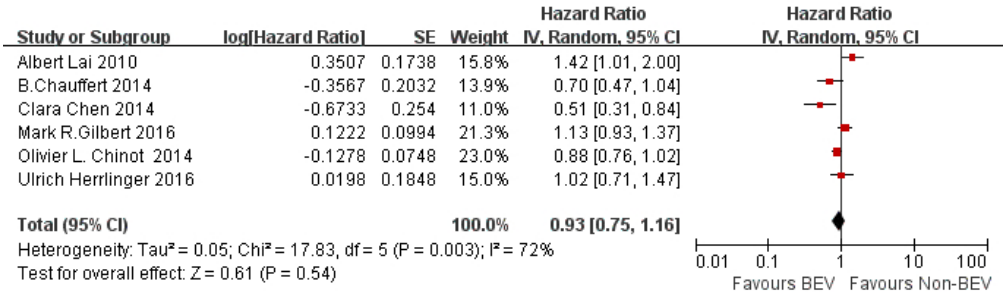


Figure 5:HR of median OS in BEV group and Non-BEV group in the treatment of glioma

144x44mm (120 x 120 DPI)

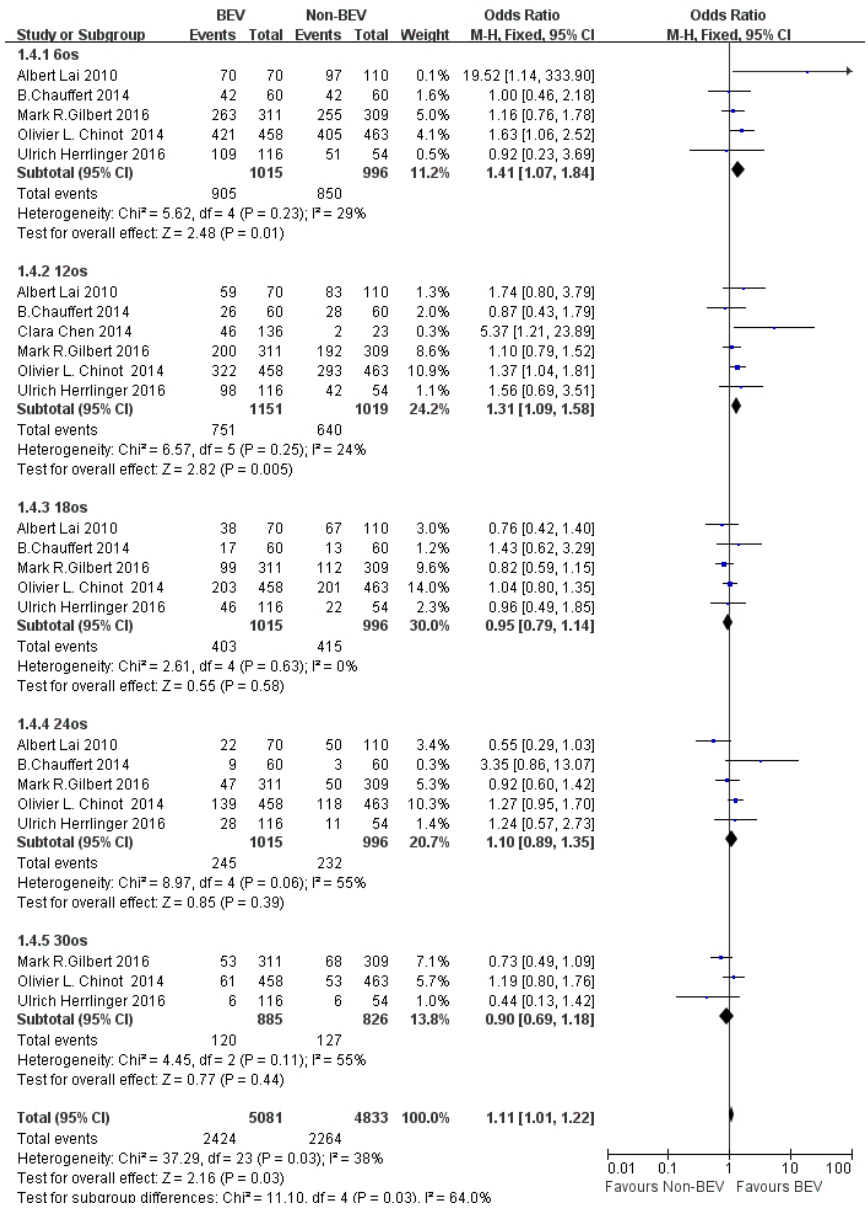


Figure 6: OR of OS at each follow-up time in the treatment of glioma in the BEV group and Non-BEV group

148x206mm (120 x 120 DPI)

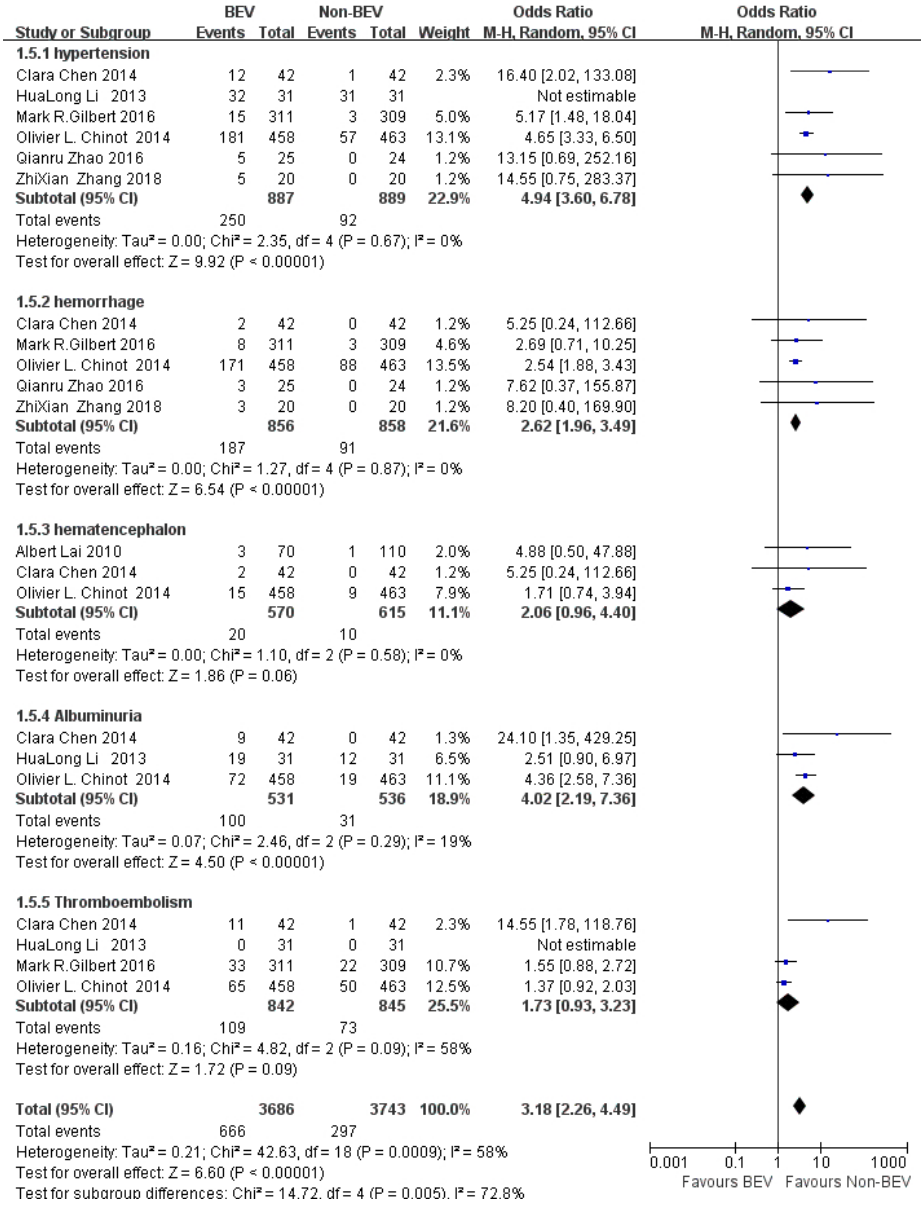


Figure 7: OR of adverse reactions in the treatment of glioma in the BEV group and Non-BEV group

150x196mm (120 x 120 DPI)

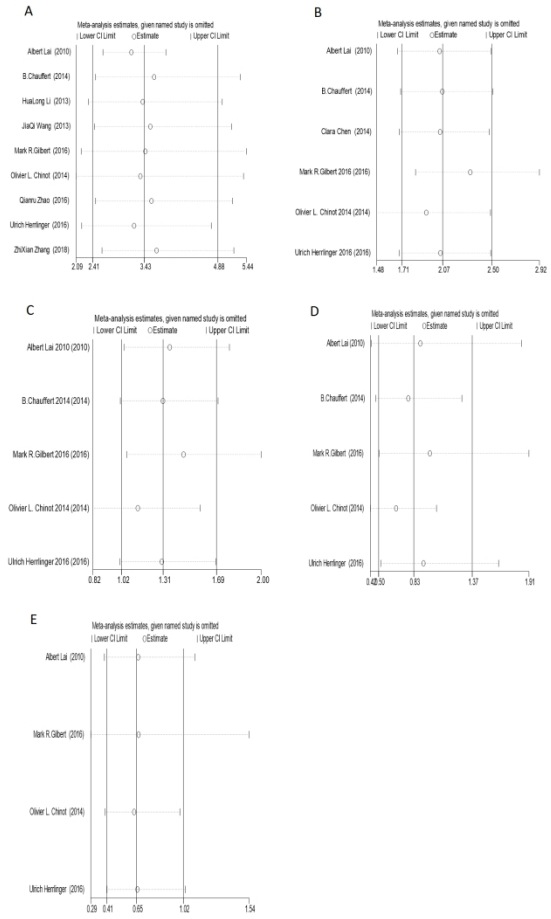


Figure 8:A: the sensitivity analysis of PFS6 ;B: the sensitivity analysis of PFS12; C:the sensitivity analysis of PFS18;D:the sensitivity analysis of PFS24;E:the sensitivity analysis of PFS30

209x296mm (288 x 288 DPI)

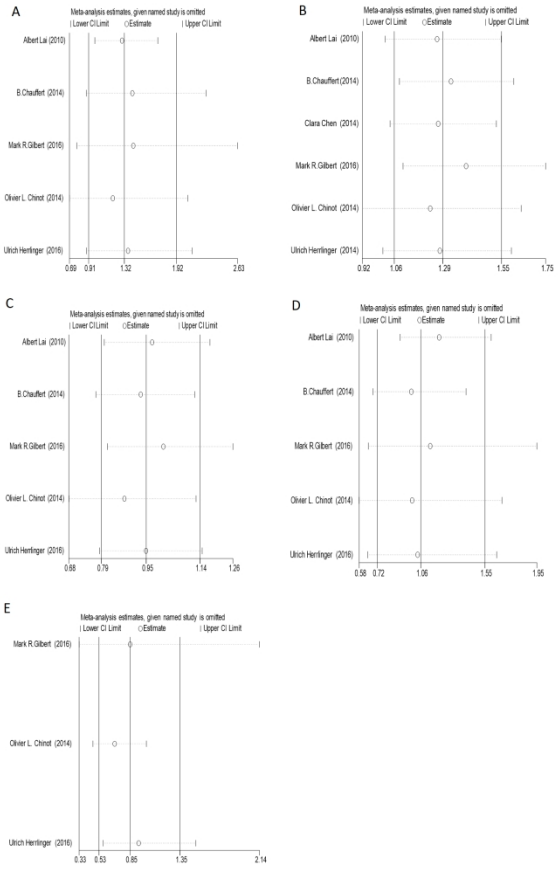


Figure 9:A: the sensitivity analysis of OS6 ;B: the sensitivity analysis of OS12; C:the sensitivity analysis of OS18;D:the sensitivity analysis of OS24;E:the sensitivity analysis of OS30

209x296mm (288 x 288 DPI)

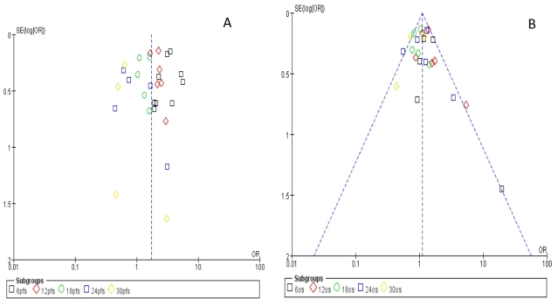


Figure 10:A: funnel chart of PFS at each follow-up time;B: funnel chart of OS at each follow-up time

209x296mm (288 x 288 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	13-14
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4-5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4-5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4-5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	5-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-8
	23b	Discuss any limitations of the evidence included in the review.	7-8
	23c	Discuss any limitations of the review processes used.	7-8
	23d	Discuss implications of the results for practice, policy, and future research.	8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	9
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	9
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	9
Competing interests	26	Declare any competing interests of review authors.	9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	9

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

BMJ Open

Efficacy and safety of bevacizumab in the treatment of adult gliomas:a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048975.R2
Article Type:	Original research
Date Submitted by the Author:	19-Aug-2021
Complete List of Authors:	Wang, huan; Xi'an Jiaotong University Medical College First Affiliated Hospital, Guo, Jianxin; Xi'an Jiaotong University Medical College First Affiliated Hospital Wang, Tianze; Xi'an Jiaotong University wang, kai; Shaanxi University of Chinese Medicine Wu, Zhuojun; Xi'an Jiaotong University Medical College First Affiliated Hospital Sun, Tianze; Xi'an Jiaotong University Medical College First Affiliated Hospital
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Patient-centred medicine
Keywords:	NEUROSURGERY, ONCOLOGY, Head & neck tumours < ONCOLOGY

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Efficacy and safety of bevacizumab in the treatment of adult gliomas:a systematic review and meta-analysis

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Keywords ： glioma, Bevacizumab, efficacy, safety, progression-free survival
Number of words:3923

ABSTRACT

Objective To assess the efficacy and safety of bevacizumab in patients with glioma.

Design Systematic review and meta-analysis.

Participants Adults aged 18 years and above, whose histology was confirmed to be malignant glioma.

Primary and secondary outcome measures: The main indicators included progression-free survival rate and overall survival rate, and the secondary indicators were adverse reactions.

Results: A total of 11 clinical center trials were included in this study for meta-analysis, including 2392 patients. The results of the meta-analysis showed that the median PFS rate of the BEV group was significantly higher than that of the Non-BEV group (P<0.00001). When comparing PFS between two groups, we found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (OR 3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (OR 2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (OR 1.31,95%CI 1.02 to 1.69, p=0.03). But at 24 months (OR 0.83, 95%CI 0.50 to 1.37, p=0.47) , there was no significant difference between the two groups. At 30 months (OR 0.62, 95%CI 0.39 to 0.97, p=0.04), the PFS of the BEV group was lower than that of the Non-BEV group. Moreover, The results showed that BEV had no significant effect on improving OS, but the adverse reaction in BEV group was significantly higher than that in non-BEV group.

Conclusion: The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the subgroup of patients, the change of recurrence mode, the optimal dose of drug, the increase of hypoxia, the enhancement of invasiveness and so on. Therefore, it is necessary to carry out more samples and higher quality large-scale research in the future.

Strengths and Limitations of this study

1. We used the Cochrane criteria to assess the risk of bias.
2. The heterogeneity was explored by sensitivity, sub-group.

3. the quality of included studies was largely moderate to high.
4. The preoperative symptoms and the scope and degree of surgical resection are not taken into account.

INTRODUCTION

Brain glioma is the most common primary intracranial tumor, accounting for about 27% of central nervous system tumors and 80% of intracranial malignant tumors[1]. The median survival time reported with brain glioma is 14-16 months[2]. The Surgical intervention combined with radiotherapy and chemotherapy are often followed for treatment of such cases, but because of its high invasive nature, it often relapses in a short time with poor prognosis. The emergence of temozolomide has considerably delayed the development of glioma to some extent, but the survival rate and quality of life of patients are still very low. Therefore, looking for better drugs to prevent and delaying the postoperative recurrence of glioma have become the focus of current research. In recent years, more and more studies have shown that malignant glioma is the tumor with the highest degree of vascularization[3]. The nature of proliferation is characterized by obvious proliferative vascular lumen and with abnormal proliferation of neovascularization which participates in the construction of tumor microenvironment[4]. It is closely related to the growth, invasion, and metastasis of the tumor, and positively correlated with the extent of malignancy and prognosis of the tumor. Recently, the unique biological characteristics of gliomas indicated that angiogenic factors may play an important role in its treatment and have become the focus of research.

Humanized anti-vascular endothelial growth factor monoclonal antibody-bevacizumab[5], as a representative drug of anti-angiogenic therapy, was approved for recurrent glioblastoma by FDA in 2009[6] and was listed in China in 2010 by CFDA. According to the radiological response rate, bevacizumab has been approved for recurrent glioblastoma in the United States and many other countries[7,8]. Although bevacizumab (BEV) has become an important part of HGG therapy, the safety and long-term efficacy of BEV are not clear. Therefore, we conducted a clinical meta-analysis to evaluate the safety and adverse reactions of BEV in patients with HGG, in order to provide a reference for clinical application.

METHODS

This study was mainly based on the literature research, hence there is no need for ethical identification.

Patient and Public Involvement

No patients or members of the public were involved in the design or conduct of this study

Search strategy

We collected all the clinical experimental studies of anti-angiogenic therapy in the treatment of gliomas, retrieved through a database search including PubMed, Embase, The Cochrane Library, WanFang, Chinese periodical full-text database (CNKI), and Chinese biomedical literature service system (CBM), the time span is from the establishment of the database to April 2020. The search strategy followed included a combination of subject words and free words, and the retrieval strategy was determined after several pre-searches. The main search words included: "glioma", "angiogenesis inhibitors", "vascular endothelial growth factors", "VEGF", and "clinical study". Additionally, we also manually searched the reference list of all articles on this topic to check and enhance the retrieval of other related publications. All search results are evaluated according to the (PRISMA) statement of "preferred reporting items for systematic review and meta-analysis".

Selection criteria

Studies were included if they fulfilled the following criteria: (1) Study subjects: the participants were adults aged 18 years and above, whose histology was confirmed to be malignant glioma. They may have undergone some form of surgery to achieve histological diagnosis (biopsy or resection); (2) Study type: The clinical control study; (3) Intervention: bevacizumab group must include bevacizumab, which can be used alone or in combination with multiple drugs. The control group (Non-BEV) refers to treatment that did not include anti-angiogenesis agents, which can be placebo or supportive therapy, or active intervention (such as chemotherapy). (4) Outcome indicators: included in accordance with the following arbitrary outcome indicators:①main indicators: progression-free survival rate, defined as the time from randomization to death or disease progression of any cause, and overall survival rate, defined as the time from randomization to death. ② key indicators: adverse events classified according to the World Health Organization (WHO) or the General terminology Standard of the National Cancer Institute (NCI-CTCAE (CTCAE2017)), including the percentage of treatment-related deaths.

Studies were excluded if they fulfilled the following conditions: Non-clinical control studies, incomplete abstract information, conference papers, reviews, and case reports. In addition, the literature of repeated publication and incomplete data that cannot extract valid data were excluded.

Data extraction

Literature screening, data extraction, and cross-checking were carried out by two independent researchers according to the initial inclusion and exclusion criteria, if there were any differences, they were discussed or judged with the assistance of a third person. For missing data, we contacted the author if possible. During the literature screening, the title and the abstract were read initially, after excluding obviously irrelevant literature, the full text was read to determine whether to include it or not. Upon matching the inclusion criteria of requirements, the following contents were extracted: (1) the basic information, including title, author, published country, publication date, research type; (2) study subjects, including the number of cases in each group, average age; (3) interventional factors, including the specific details of exposure factors, follow-up time, etc.; and (4) the outcome indicators.

Quality assessment

Using the Cochrane collaboration tool, the risk of bias in individual studies was assessed from seven aspects (sequence generation, allocation hiding, uninformed participants and people, incomplete outcome data, selective reports, and other biases and risks) [9]. Finally, each project was evaluated at three levels: low risk, unclear, and high risk. The two authors conducted independent quality assessments and any differences among them were resolved through discussions with a third research expert.

Statistical analysis

Analysis of outcome index

PFS, OS, and adverse reactions were analyzed by Meta with RevMan5.1 software. The dichotomy data is expressed as the combined risk ratio (RR) or risk ratio (hazard ratio; HR),The measurement data is expressed as the mean difference (WMD).The interval estimation was expressed by 95%CI, and the test level of the effect quantity was α = 0.05.The test for heterogeneity used I^2 statistics. If there is no significant heterogeneity among studies ($I^2 \leq 50\%$), we used the fixed effects model for data consolidation. While there is significant heterogeneity ($I^2 > 50\%$) between the results of the study, the random effects model for data analysis would be used.

Sensitivity analysis

Simultaneously, stata15.1 was used for sensitivity analysis,adopt the method of examining the impact of individual studies and eliminate them one by one, if the

value obtained is within the confidence interval on both sides, the result is stable.otherwise, they were regarded as unstable. If the results are unstable, it is proved that the elimination research has a great impact on the overall research results. We will conduct a professional analysis of the elimination research to find out the reasons for its impact on the results and study it. Studies included in literature > 10 were used to detect publication bias by funnel chart.

RESULT

Literature screening

A total of 1108 related literature were obtained in the initial examination. After screening the literature one by one, a total of 1123 patients were included in 11 clinical studies[10-20].The flow chart and the results of literature retrieval are shown in figure 1.

The basic characteristics of the inclusion study

For the inclusion study, the basic information for inclusion is completed using pre-developed forms (Tables 1, 2).

Table 1: basic information for inclusion in the study

Study	State	Research type	Cases (experimental/ control)	Ages(experimental / control)	Follow-up time	Outcome
Olivier L. Chinot, M.D[2014][10]	France	RCT	458/463	20-84/18-79	The last patient was hospitalized for 17 months.	1and2year survival rates、safety and quality of life、PFS、OS
Qianru Zhao[2016][11]	China	RCT	25/24	24-71/27-	The median follow-up time was 7.9 months	disease control rate、median survival time、OS、PFS

Ulrich Herrlinger[2016][12]	Germany	RCT	116/54	25–78/26–78	Long-term follow-up until death	PFS–6、PFS、OS
Mark R.Gilbert 2016[13]	Germany	RCT	320/317	>18	6 cycles	OS、PFS
Clara Chen 2014[14]	America	Non-RCT	57/79/23	30–77/24–82/19-78	>1year	OS、PFS、Adverse reactione
Hualong Li [2020][15]	China	RCT	31/31	18–70/19–69	4 months	PFS6、DCR、Adverse reaction
Zhixian Zhang 2018[16]	China	RCT	20/20	24–74	5.2–18months	PFS6、OS12
Jiaqi Wang[2013][17]	China	RCT	27/27	53.6 ± 9.7/54.7±8.8	6months–2years	RR、DCR、Adverse reaction
Albert Lai[2010][18]	America	RCT	70/110	31.3–75.8/20.5–90	>42months	OS、PFS、Adverse reaction
B.Chauffert[2014][19]	Britain	RCT	60/60	43–69/43–71	6 months	OS、PFS、Adverse reaction
Carmen Balana[2016][20]	Spain	RCT	48/45	36–75/43–75		OS、PFS、Adverse reaction

Table 2: basic characteristics of the inclusion study

Study	Male	Female	Open biopsy	Partial resectio	Complete resection	experimental/ control
Olivier L. Chinot, M.D[2014]	282（61.6）/298（64.4）	176（38.4）/165（35.6）	60（13.1）/44（9.5）	210（45.9）/223（48.2）	188（41.0）/196（42.3）	Bevacizumab+RT－TMZ/ Placebo+RT－TMZ
Qianru Zhao[2016]	14/12	11/12	/	15/16	10/8	BEV+TMZ/TMZ
Ulrich Herrlinger[2016]	80(69.0)/34(63.0)	36(31.0)/20(37.0)	0/2(3.7)	58(50.0)/27(50.0)	58(50.0)/25(46.3)	BEV+IRI/TMZ
Mark R.Gilbert 2016	/	/	/	/	/	Bevacizumab/ Placebo
Clara Chen 2014	30(53)/45(57)/15(65)	57/79/23 27(47)/34(43)/8(35)	34(60)/44(56)/14(61)	20(35)/33(42)/9(39)	3(5)/2(2))/0(0)	Bevacizumab monotherapy /Bevacizumab combination /Nonbevacizumab
Hualong Li[2020]	19/18	12/13	/	/	/	TMZ+BEV/TMZ

Zhixian Zhang 2018	22	18	/	18	22	BEV+TMZ/ Gamma knife +TMZ/
Jiaqi Wang[2013]	16/14	11/13	/	/	/	TMZ+BEV/TMZ
Albert Lai[2010]	31/40	39/70	2/23	40/40	28/47	RT+TMZ+BV/UC LA/KPLA Control RT/TMZ
B.Chauffert[2014]	26/23	34/37	/	/	/	BEV+IRI/TMZ+RT
Carmen Balana	31/25	17/20	42/35	/	/	TMZ+BEV/TMZ

Risk of bias assessment

The results of the bias risk assessment included in the study are shown in figure 2.

Meta-analysis results

Progression-free survival

Seven studies[10,12-14,18-20] reported median progression-free survival (BEV group, n=1160) and Non-BEV group (n=1027).There was no significant difference in the heterogeneity test (I^2=34%<50%), so the fixed effect model was used for data analysis.Results suggested that the median progression-free survival of gliomas treated with BEV was significantly longer than that of malignant gliomas treated with Non-BEV (HR0.71, 95%CI, 0.65 to 0.78,P<0.00001), As shown in figure 3.

Ten studies[10-19] compared PFS ratios at different follow-up between the Bev group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=71%>50%), so the random effect model was used. Through the results found it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (OR 3.31, 95%CI 2.74 to 4.00, p<0.00001), 12

months (OR 2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (OR 1.31,95%CI 1.02 to 1.69, p=0.03).But at 24 months (OR 0.83, 95%CI 0.50 to 1.37, p=0.47), P > 0.05, so there was no significant statistical difference between the two groups.At 30 months (OR 0.62, 95%CI 0.39 to 0.97, p=0.04), 0.61 < 1, the diamond pattern falls on the group that supports Non-BEV group,so the PFS of the BEV group was lower than that of the Non-BEV group.as shown in figure 4.

Overall survival time

Seven studies[10,12-14,18-20] reported the median overall survival time, and there was a significant difference in the total heterogeneity test (I^2=71%>50%)，so the random effect model was used. Results suggesting that there was no significant difference in median overall survival time between the BEV group and Non-BEV group (HR0.90, 95%CI, 0.73 to 1.10,P=0.30), as shown in figure 5.

Six studies[10,12-14,18-19] compared OS ratios at different follow-up between the Bev group and the Non-BEV group. there was no significant difference in the heterogeneity test (I^2=38%<50%), so the fixed effect model was used for data analysis. Through the results found it was found that the OS in the BEV group was higher than that in the Non-BEV group at 6 months(OR 1.41；95%CI，1.07-1.84；P=0.01),12 months(OR 1.31；95%CI，1.09-1.58；P=0.005).But at18 months （OR 0.95；95%CI，0.79-1.14；P=0.58），24 months（OR 1.10；95%CI，0.89-1.35；P=0.39），and 30 months（OR 0.90；95%CI，0.69-1.18；P=0.44), P > 0.05, so there was no significant statistical difference between the two groups,as shown in figure 6.

Adverse reaction

As shown in figure7, there were six studies[10-11,13-15] that compared adverse reactions between the BEV group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I^2=54%>50%), and the random effect model was used. The results showed the combined OR values of hypertension, hemorrhage, hematencephalon, albuminuria, and thromboembolism as follows: hypertension (OR 5.14, 95%CI 3.79 to 6.96, P<0.00001), hemorrhage (OR 2.62, 95%CI 1.96 to 3.49, P<0.00001), hematencephalon (OR 2.26, 95%CI 1.08 to 4.72, P=0.03), albuminuria (OR 4.04, 95%CI 2.56 to 6.37, P<0.00001) and thromboembolism (OR 1.57, 95%CI 0.88 to 2.77, P=0.13).Through the results found it was found that the adverse reactions in the BEV group was higher than that in the Non-BEV group .

Sensitivity analysis

The sensitivity test was used to evaluate the stability of OS, PFS, and adverse reactions in the included literature, which showed that all values remained in the

confidence interval on both sides after one by one elimination. Hence, it can be concluded that all the included literature is stable, as shown in figures 8,9.

Publication bias

As shown in figures 10, the funnel chart was mainly concentrated at the top. Moreover, the symmetry was also proper, so it was concluded that the possibility of publication bias was small.

DISCUSSION

According to histopathological and clinical features, gliomas are divided into astrocytoma, oligodendroglioma, oligodendroglioma and ependymoma, which are the most common malignant tumors derived from neuroepithelium. Although the technical level of surgery, radiotherapy and chemotherapy[21] in the treatment of glioma has been greatly improved, but the recurrence rate and mortality rate are still high，so there is an urgent need for a new treatment. Glioma affects the body through a variety of pathophysiological processes, in which angiogenesis plays an important role in the occurrence and development of glioma, so blocking angiogenesis has become a new direction of treatment. Bevacizumab is an anti-(VEGF) antibody against vascular endothelial growth factor[22], which acts mainly by competing against VEGF, and binding to VEGFR on the target cell membrane. Pope[23] and other studies have shown that the high surface of VEGF affects blood vessel density and tumor grade. Some studies have shown that Ang2/Tie2[24,25] and STAT3[26] are two important signal pathways in anti-angiogenic therapy, which play a good role in inhibiting peritumoral edema and the increase of neurological symptoms. In order to better understand the advantages and disadvantages of BEV on glioma, this study has a better understanding of the efficacy and safety of BEV through systematic review.

The results of our study showed that the PFS of BEV group was higher than that of Non-BEV group during the follow-up period of < 18 months, but when the follow-up time was 30 months，the PFS of BEV group was lower than that of Non-BEV; meanwhile，It was found that the OS in the BEV group was higher than that in the Non-BEV group at 6 months,12 months， but after 12 months, there was no statistically significant difference between the BEV group and the non-BEV group. The study of Li YD[27] showed that the progression-free survival time at 24 months and 36 months in the bevacizumab group was lower than that in the non-bevacizumab group; The results of LiaoKL[28] showed that a higher incidence of PFS could be obtained by adding BEV to newly diagnosed GB, and this combined treatment did not improve OS. The AVAglio[29] trial showed that patients treated with bevacizumab had significant advantages in PFS (6.2 months vs. 10.6 months) and

maintenance of life quality, but showed no advantages in OS (16.8 months vs. 16.7 months).2.2% of patients treated with bevacizumab confirmed false progression, compared with 9.3% of patients treated with non-bevacizumab.Vredenburgh[30] found in a single-group clinical phase 2 experimental study that the median PFS of bevacizumab combined with temozolomide and radiotherapy reached nearly twice the standard of 3-14 months, however the overall survival was not significant Improvement.Chinot[31] and Gilbert[32] conducted phase 3 clinical trials with a placebo control group, the results showed that PFS increased by 40%-71% compared with the control group. Special related research on OS, Brandes[33] and Wick[34] also found that BEV failed to improve OS of patients with glioma in a randomized study analyzing bevacizumab. From the above research, BEV can improve the PFS of glioma patients within 18 months, but the PFS of patients may be reduced after 30 months. It has no obvious significance to improve OS.

This study showed that after the application of BEV, there were five common adverse reactions: hypertension, hemorrhage, hematencephalon, albuminuria and thromboembolism. A phase II trial of Japanese[35] showed that the most common side effects were albuminuria, hypertension, hemorrhage, fever and epilepsy. Studies[36] showed that the incidence of adverse reactions above grade 3 was 27.1% to 46.4%, the most common events were thromboembolism, hypertension, epilepsy, fatigue and intestinal perforation. Zhang Li[37] searched 20 articles about adverse reactions caused by BEV, and found that the main adverse reactions were cardiovascular and hematological diseases. Norden[38] evaluated 64 glioma patients who received BEV anticoagulant therapy and 64 glioma patients who did not receive anticoagulant therapy, The results showed that the incidence of intracranial hemorrhage and other bleeding in patients treated with anticoagulants was significantly higher than that in patients with BEV alone, but the incidence of severe intracranial hemorrhage was within an acceptable range.Therefore, when using bevacizumab clinically, it is necessary to closely observe drug adverse reactions, monitor blood pressure, coagulation function and other indicators, and deal with symptoms in time.

From the above research results, it can be concluded that long-term use of BEV does not increase the patient's PFS, BEV can improve the PFS of glioma patients within 18 months, but the PFS of patients may be reduced after 30 months. Nagham Kaka found[39] that BEV could have a role in the treatment of particular subgroups of patients with newly diagnosed GBM. Several studies[40,41] have found that the median PFS of patients with methylation is longer than that of MGMT unmethylated tumors treated with RT and TMZ combined with BEV. Sandmann and colleagues[42] found that BEV combined with standard TMZ and RT can improve the survival rate of

neurotumors, while poorly differentiated mesenchymal tumors may make tumors resistant to BEV over time. Adilijiang and Colleagues[43] found that treatment with BEV and TMZ results in the upregulation of certain microenvironment related genes in IDH1 mutant tumors in vitro, specifically those involving immune response and extracellular matrix organization. Therefore, The question of whether the limitation of BEV in the treatment of gliomas is due to fixed subsets deserves constant attention.

Studies have shown[44,45] that antiangiogenic therapy can lead to a transition of glioma to a more aggressive phenotype. In retrospective analysis[46,47] a trend toward enhanced infiltra-tive disease was seen in bevacizumab-treated glioma patients suggesting that enhanced tumor inhibition may be a conse-quence of VEGF signaling blockade. Shiao-Pei Weathers[48] shows that determining the best biological dose and the subgroup of patients most likely to obtain long-lasting benefits can improve the durability of bevacizumab. Victor A Levin[49] found treatment for recurrent GBM with BEV appears to improve survival at a dose lower than that in the FDA drug insert. Study[50] suggest that the higher dosage of BEV utilized may have impacted survival benefits. Animal models[51] also suggest that higher dose of anti-VEGF treatment, resulting in more hypoxia, may increase tumor aggressiveness. Ryota Tamura[52] found that high doses and long-term use of anti-VEGF/VEGFR may lead to hypoxia. Shiao-Pei Weathers[48] proposed in tumors where excessive vascular pruning takes place, hypoxia exacerbated by antiangiogenic therapy is likely responsible for initiating a cascade of events. As mentioned above, there are many possible reasons for the limited efficacy of antiangiogenic therapy. But The lack of a long-lasting response to current antiangiogenic treatment underscores the need for a better understanding of how to use antiangiogenic therapy to optimize radiation and chemotherapy treatments.

CONCLUSIONS

The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the subgroup of patients, the change of recurrence mode, the optimal dose of drug, the increase of hypoxia, the enhancement of invasiveness and so on. BEV treatment has no obvious meaning in improving OS, and it has some side effects, which are acceptable, but we still need to pay close attention to it and take active measures to reduce the side effects. Therefore, it is necessary to carry out more samples and higher quality large-scale research in the future.

Declaration:

Contributors WH and GJX contributed to conception and design. WH、WTZ and WK contributed to data acquisition or analysis and interpretation of data. WH、GJX、WTZ、WZJ and STZ were involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Funding This study was funded by The First Affiliated Hospital of Xi'an Jiaotong University. The funder had no role in the design of the study, the collection, analysis or interpretation of data, the writing of the report or the decision to submit the paper for publication. Award/Grant number is not applicable.

Ethics Approval This study belongs to data research and is not applicable to ethical review.

Competing interests None declared.
Competing interests of Reviewer: None

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing All data relevant to the study are included in the article or uploaded as supplementary information.

All the illustrations are as follows:

Figure 1: document screening process and results

PubMed (n=259), The Cochrane Library (n=153), EMbase (n=155), CNKI (n=118), CBM (n=358), WanFang (n=65).

Figure 2: bias risk assessment form

Figur 3:HR of median PFS in BEV group and Non-BEV group in the treatment of glioma

Figur 4:OR of PFS at each follow-up time in BEV group and Non-BEV group in the treatment of glioma

Figure 5:HR of median OS in BEV group and Non-BEV group in the treatment of glioma

Figure 6: OR of OS at each follow-up time in the treatment of glioma in the BEV group and Non-BEV group

Figure 7: OR of adverse reactions in the treatment of glioma in the BEV group and Non-BEV group

Figure 8:A: the sensitivity analysis of PFS6 ;B: the sensitivity analysis of PFS12; C:the sensitivity analysis of PFS18;D:the sensitivity analysis of PFS24;E:the sensitivity analysis of PFS30

Figure 9:A: the sensitivity analysis of OS6 ;B: the sensitivity analysis of OS12; C:the sensitivity analysis of OS18;D:the sensitivity analysis of OS24;E:the sensitivity analysis of OS30

Figure 10:A: funnel chart of PFS at each follow-up time;B: funnel chart of OS at each follow-up time

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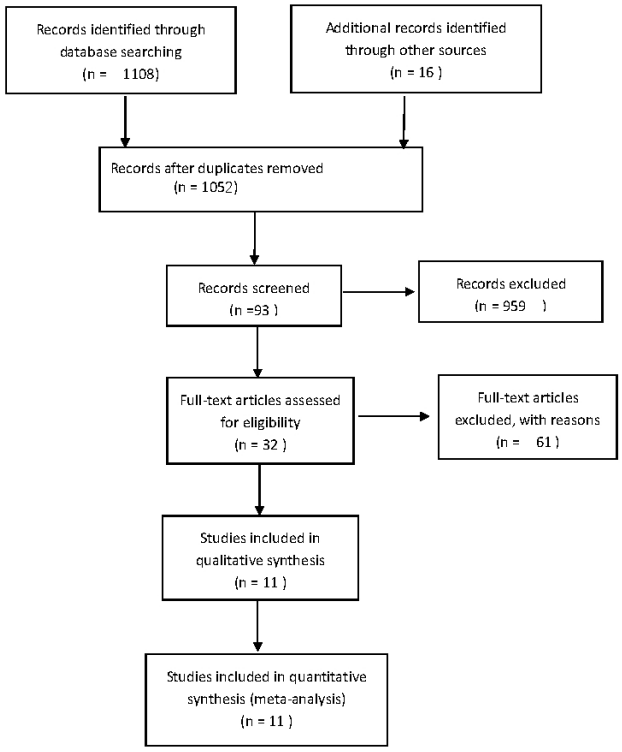

Figure 1: document screening process and results

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PubMed (n=259), The Cochrane Library (n=153), EMbase (n=155), CNKI (n=118), CBM (n=358), WanFang (n=65).

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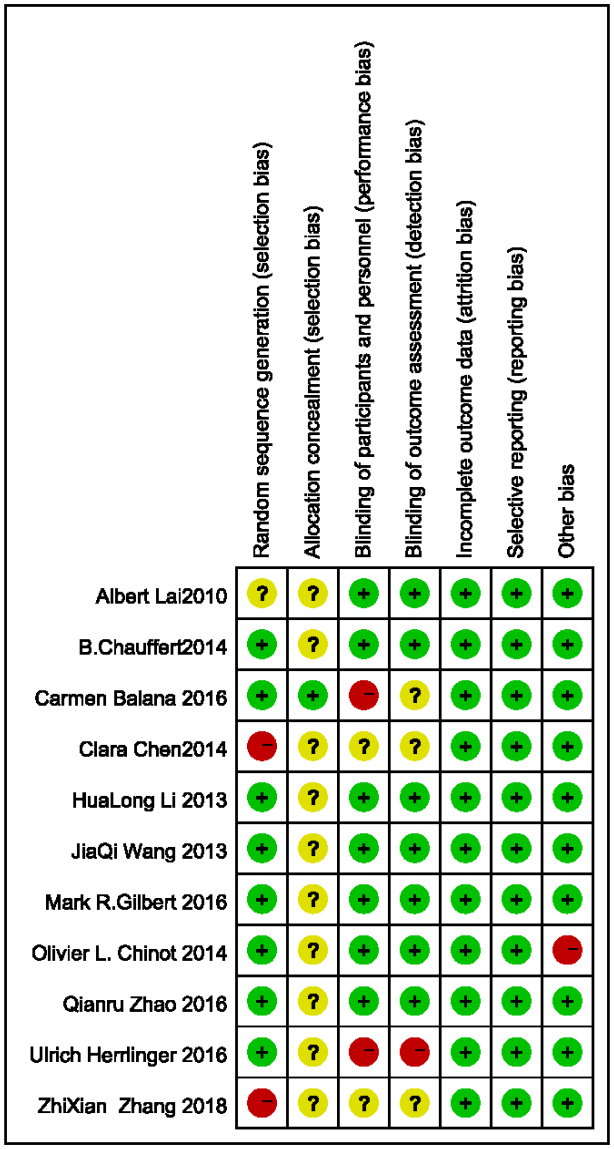

Figure 2: bias risk assessment form

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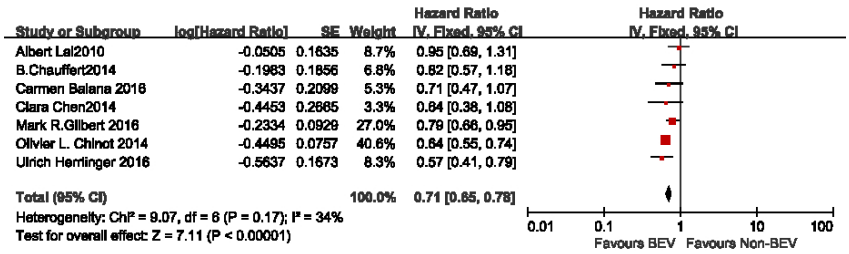

Figur 3:HR of median PFS in BEV group and Non-BEV group in the treatment of glioma

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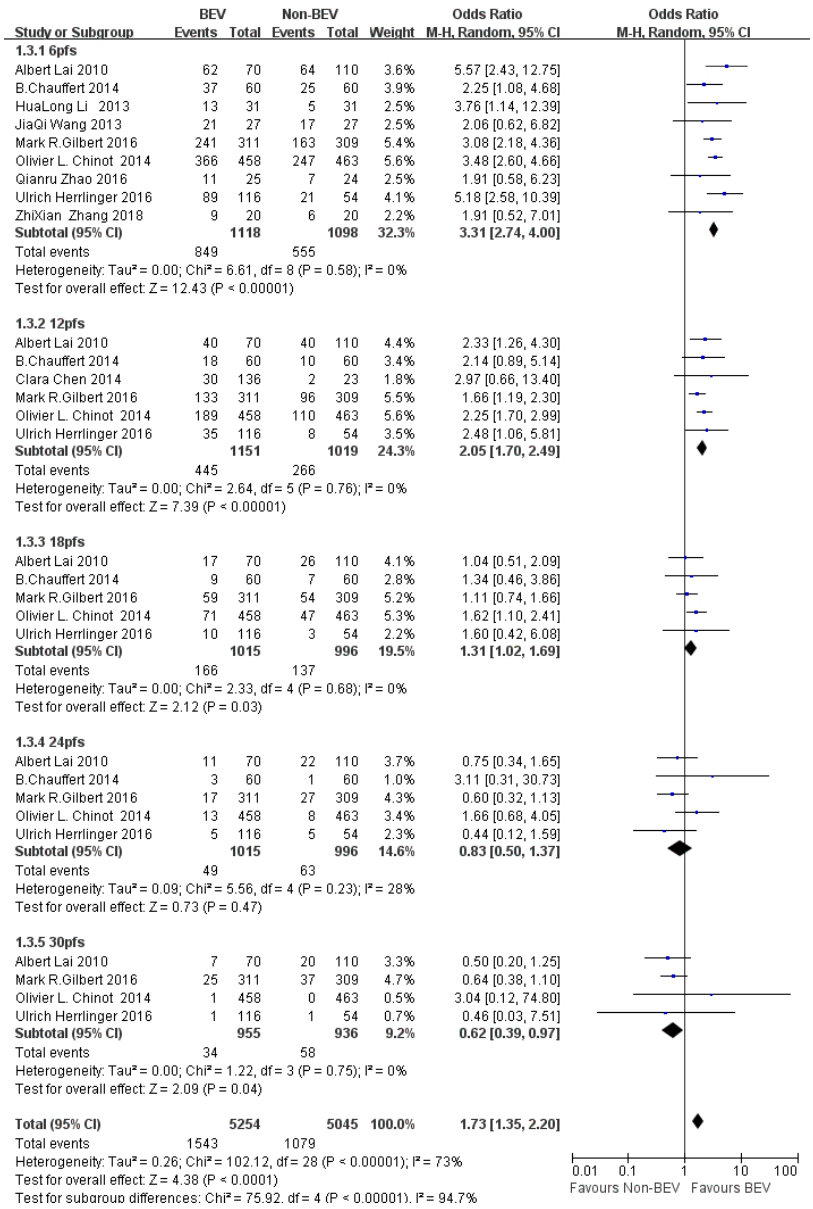

Figur 4:OR of PFS at each follow-up time in BEV group and Non-BEV group in the treatment of glioma

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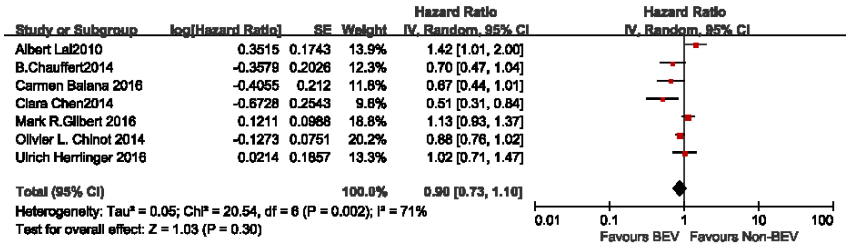

Figure 5:HR of median OS in BEV group and Non-BEV group in the treatment of glioma

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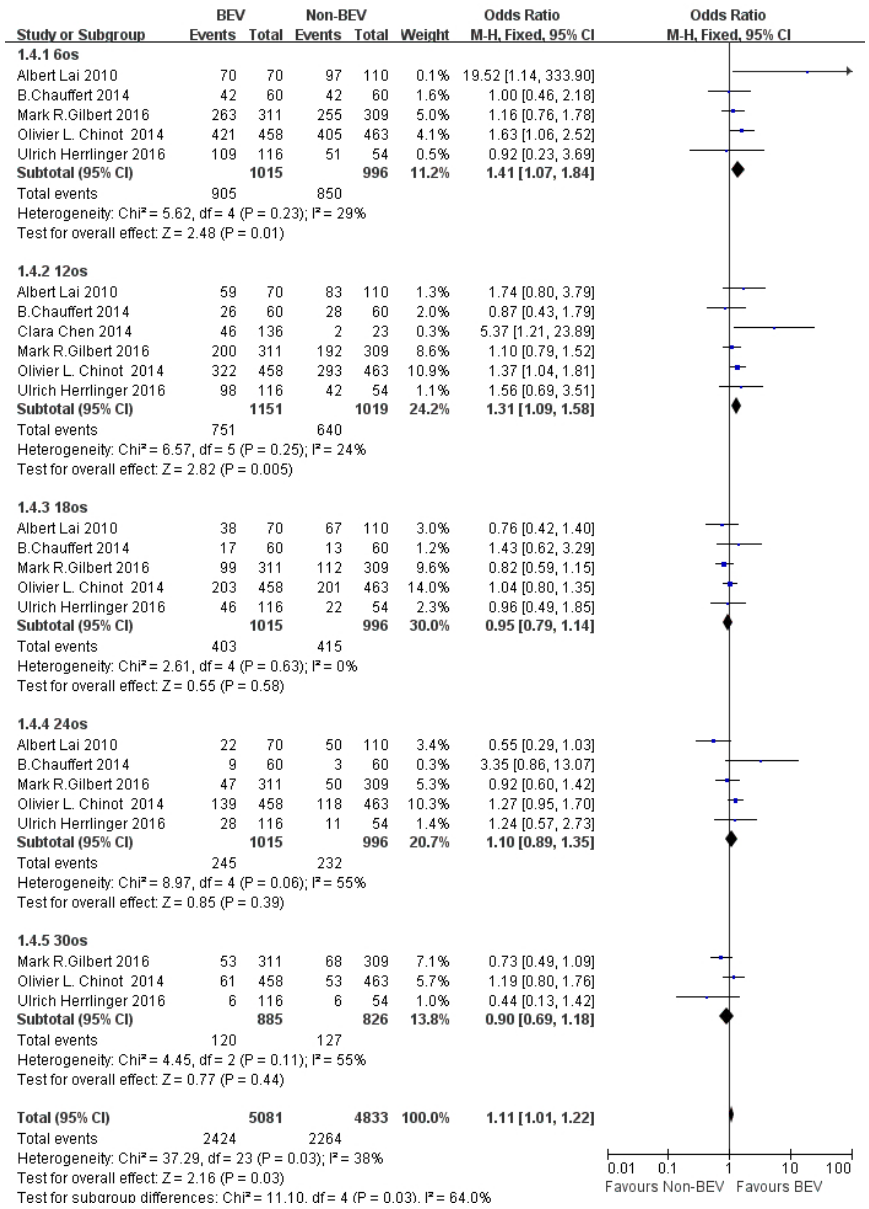

Figure 6: OR of OS at each follow-up time in the treatment of glioma in the BEV group and Non-BEV group

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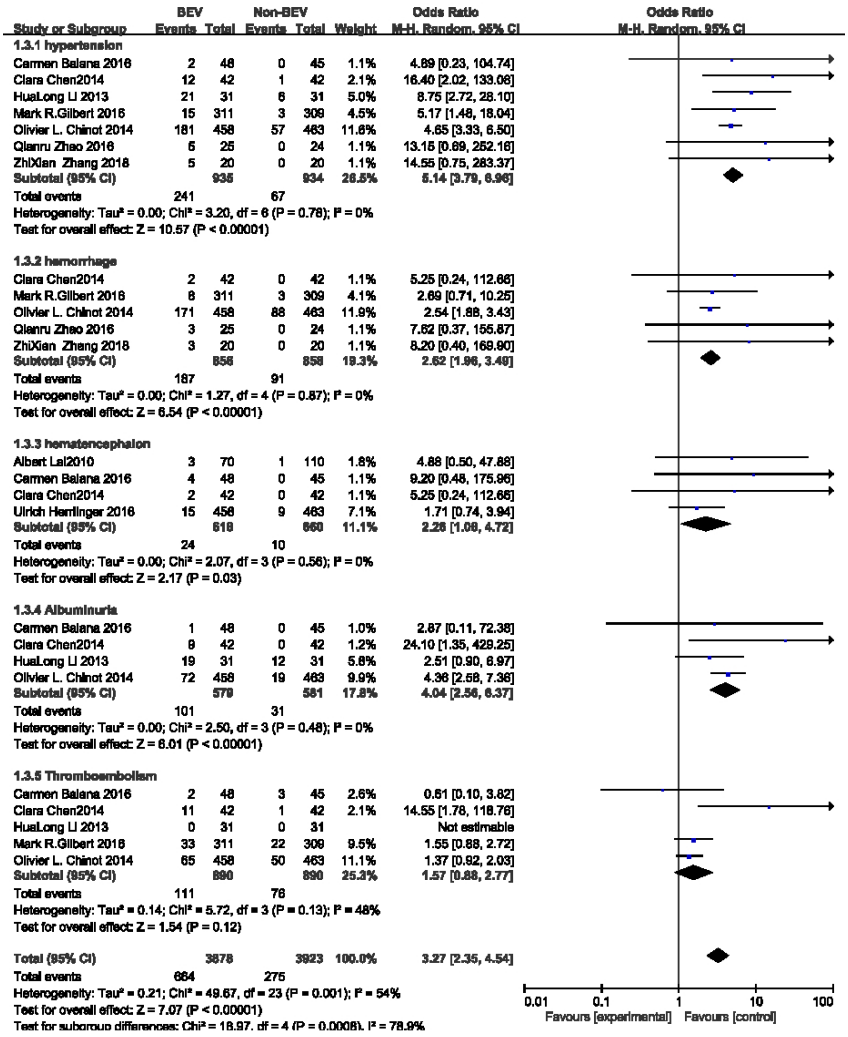

Figure 7: OR of adverse reactions in the treatment of glioma in the BEV group and Non-BEV group

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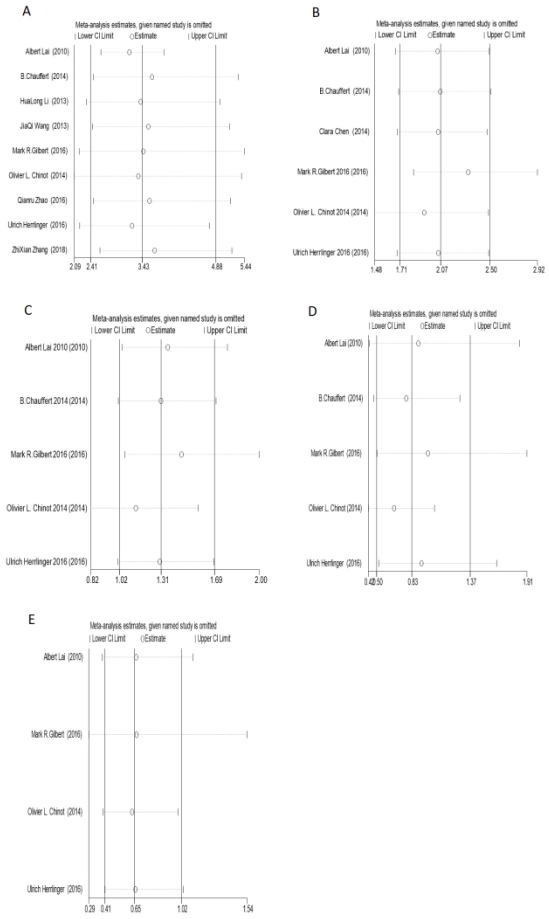

Figure 8:A: the sensitivity analysis of PFS6 ;B: the sensitivity analysis of PFS12; C:the sensitivity analysis of PFS18;D:the sensitivity analysis of PFS24;E:the sensitivity analysis of PFS30

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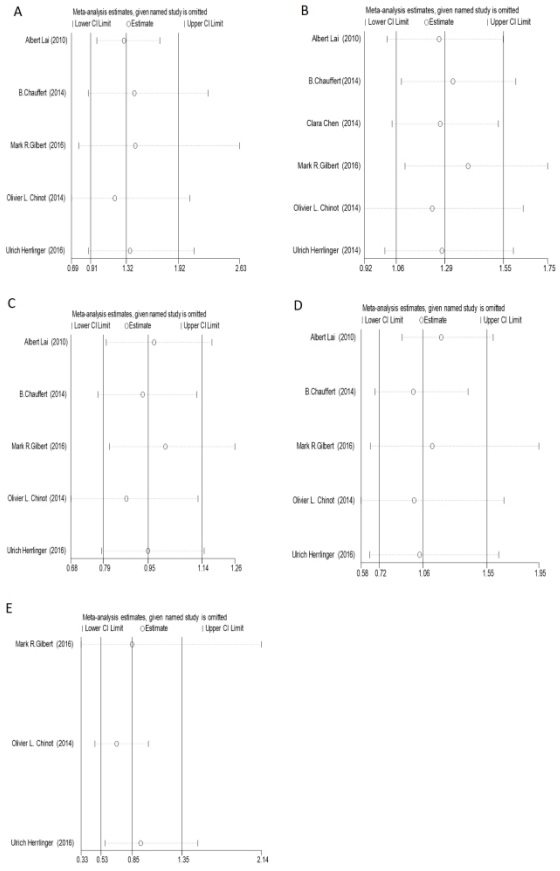

Figure 9:A: the sensitivity analysis of OS6 ;B: the sensitivity analysis of OS12; C:the sensitivity analysis of OS18;D:the sensitivity analysis of OS24;E:the sensitivity analysis of OS30

209x296mm (288 x 288 DPI)

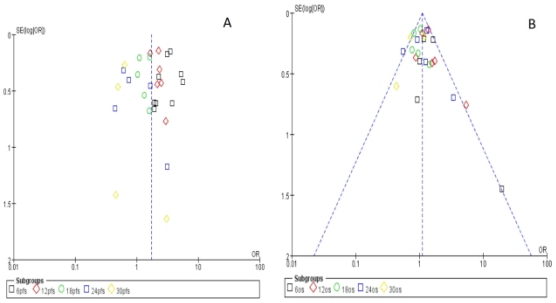

Figure 10:A: funnel chart of PFS at each follow-up time;B: funnel chart of OS at each follow-up time

209x296mm (288 x 288 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	13-14
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4-5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4-5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4-5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	5-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-8
	23b	Discuss any limitations of the evidence included in the review.	7-8
	23c	Discuss any limitations of the review processes used.	7-8
	23d	Discuss implications of the results for practice, policy, and future research.	8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	9
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	9
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	9
Competing interests	26	Declare any competing interests of review authors.	9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	9

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71