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Original Article

Radiotherapy plus procarbazine, lomustine, and vincristine versus radiotherapy alone for glioma: a meta-analysis of randomized controlled trials

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Abstract: Recent studies have shown that radiotherapy (RT) plus procarbazine, lomustine, and vincristine (PCV) is more effective for the treatment of gliomas than RT alone. The aim of our meta-analysis is to compare the efficacy of RT plus PCV versus RT alone for the treatment of glioma patients after surgery. We searched the randomized controlled trials (RCTs) investigating the curative effect of RT plus PCV versus RT alone for glioma patients after surgery in PubMed, EMBASE and Cochrane library. The evaluation indexes including hazard ratios of overall survival (OS) and progression-free survival (PFS). Individual hazard ratios with 95% confidence intervals (CIs) were pooled analyzed. Four RCTs were included with 1,584 patients in this meta-analysis. The results showed that RT plus PCV will had a longer OS (HR = 0.83, 95% CI 0.74-0.94) and a longer PFS (HR = 0.77, 95% CI 0.69-0.87) than RT alone in the treatment of patients with gliomas. RT combined with PCV chemotherapy could improve OS and PFS of patients with glioma after surgery. Further investigations are required to confirm these findings.

Keywords: Glioma, lomustine, meta-analysis, procarbazine, radiotherapy, vincristine

Introduction

Glioma is the most common primary central nervous system tumors, which accounting for about half of all primary brain tumors and 77% of malignant tumors [1-3]. The first choice for the treatment of gliomas is surgery. However, complete resection is difficult because of the tumor present an invasive growth characteristics and has no obvious boundary between the brain tissue. Nowadays, radiotherapy (RT) plus chemotherapy after surgery is recommended as the comprehensive treatment [4]. It still remains controversial about the chemotherapy as the presence of blood-brain barrier and toxicity of chemotherapy drugs. There are a few of researches and meta-analyses which investigated the curative effect of chemotherapy in the treatment of gliomas [5-7]. These studies have explored the effects of chemotherapy depend on the characteristics of drugs and tumors.

Procarbazine, lomustine, and vincristine (PCV) are very commonly used in clinical treatment. There is now a doubt that whether adjuvant PCV therapy would improve survival rate [8, 9]. Some randomized controlled trials (RCTs) have explored the efficacy of radiotherapy combined PCV in treatment of gliomas [8, 10-12]. However, the results are still controversial. So, we performe this meta-analysis to explore whether RT plus PCV would increase the survival rate compared with RT alone for glioma patients after surgery. Moreover, we also analysis the effect of treatment and patient characteristics on the survival.

Materials and methods

Article selection and inclusion/exclusion criteria

Two independent authors searched the PubMed, EMBASE and Cochrane library for relevant randomized controlled trials (RCTs) published up to December 1, 2015. The key words included in this strategy with MeSH heading: “radiotherapy”, “procarbazine, lomustine, and vincristine”, “glioma”. The articles were limited

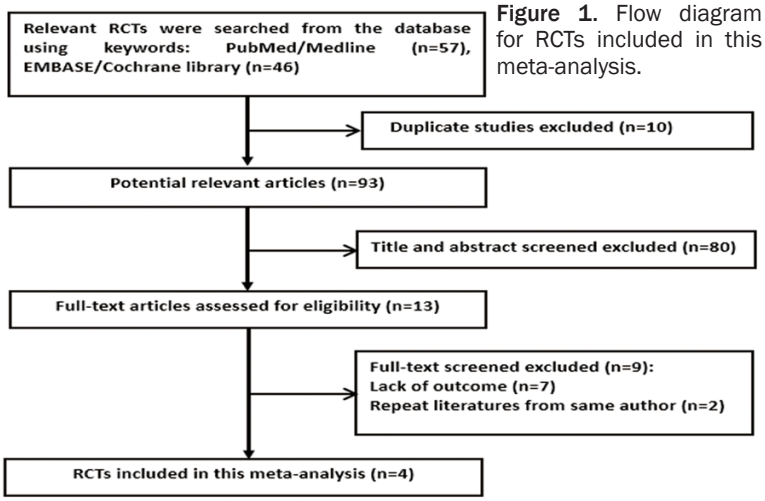

Figure 1. Flow diagram for RCTs included in this meta-analysis.

to English language and human subjects. In addition, we also checked the reference lists of identified studies for other potentially eligible trials. The RCTs included in this meta-analysis must met the following criteria: adult patients diagnosed with glioma; PCV plus RT compared with RT; PCV and RT specifically defined; and date available on the overall survival (OS) and progression-free survival (PFS). The exclusion criteria included: reviews, comments, letters, conference abstracts and case reports; patients with metastatic and recurrent glioma after surgical resection; and references lacking relevant outcome data. We used PRISMA statement as our guidance [13].

Data extraction

Two authors extracted the literature data independently. The extracted data included first author, year of publication, number of patients, main eligibility criteria, specific chemotherapy and radiotherapy, the toxic reaction on PCV, hazard ratios (HR) value of overall survival (OS) and progression-free survival (PFS). Moreover, relevant subgroup data based on the characteristics of patients and study design (i.e., pathology, performance status, RT schedule, age, extent of surgery, and molecular assessment) were also extracted. Any disagreements were resolved by discussion.

Quality assessment

The Jadad scale was used for the evaluation of methodological quality of each trial. Main point quality scales contain randomization (0-1 points), double-blind (0-1 points), description of randomization methods (0-1 points), allocation concealment (0-1 points) and follow-up reporting (0-1 points). Higher scores mean better quality of literature.

Data analysis

HR was used for the effect measure for variables which are expressed as time-to-event. In this meta-analysis, HRs with 95% confidence intervals (CIs) were conducted pooled analysis. The subgroup analyses were performed based on the characteristics of patients and study design (i.e., pathology, performance status, RT schedule, age, extent of surgery, and molecular assessment). If the subgroup data of studies from only one study, then these results would be simply listed as the single sample analyses. Chi square (χ^2) and I^2 statistics were used for the assessment of heterogeneity. The I^2 statistic of > 50% and *P* value of < 0.10 considered to have a high degree of heterogeneity. A random effect model was used to calculate the HR with 95% CI if the heterogeneity was significant, otherwise we would use the fixed effect model. It meant that there was a significant difference between RT plus PCV and RT alone when $P < 0.05$, except where otherwise specified. HRs of individual trials and overall were displayed in forest plots. The visually symmetry of Begg funnel plots were used for evaluation of potential publication bias. Moreover, the quantification of publication bias was also tested by using Begg and Egger tests [14, 15]. STATA 12.0 software was used for all statistical analysis.

Results

Study characteristics

A total of six studies met the inclusion criteria after the preliminary screening. Among them, 2 studies were excluded because of same samples. Eventually, 4 RCTs were included in this meta-analysis [10-12, 16], which involving 791 patients treated with RT alone and 793 patients treated with RT plus PCV (see **Figure 1**). The main characteristics and Jadad scores of RCTs were listed in **Table 1**. The clinical data of

Table 1. Main characteristics and Jadad score of each randomized controlled trials

Authors and publication year	Country	Study period	Study design/ Jadad score	Patients number	Median follow-up (year)
Medical Research Council Brain Tumor Working Party (2001)	United Kingdom	1988-1997	Multi-center, RCT/4	674	3 (1-8)
Shaw et al. (2012)	United States	1998-2002	Multi-center, RCT/3	251	5.9
Cairncross et al. (2013)	Canada	1994-2002	Multi-center, RCT/4	291	11.3 (0.5-16.8)
van den Bent et al. (2013)	Netherlands	1995-2002	Multi-center, RCT/4	368	11.7

patients included in this studies were listed in **Table 2**. The details of adjuvant therapy, including radiation dose and fraction of RT and the dose and time of PCV, were listed in **Table 3**.

Survival

All the 4 RCTs provided the HR of OS and PFS. The results of meta-analysis showed that RT plus PCV group had a longer OS than RT alone group (HR = 0.83, 95% CI 0.74-0.94) (see **Figure 2**). The heterogeneity among these trials was significant (χ^2 = 5.96, I^2 = 49.7%) and the random effect model was used. The HR of PFS in the RT plus PCV group was also lower than it in the RT alone group (HR = 0.77, 95% CI 0.69-0.87) (see **Figure 3**). The heterogeneity among these trials was significant (χ^2 = 8.63, I^2 = 65.2%) and the random effect model was used.

Publication bias

The interpretability of publication bias assessed by Begg and Egger tests with only 4 studies were limited. The risk of publication bias was also evaluated by the symmetry of the funnel plot, which suggested that publication bias was not obvious in this meta-analysis.

Toxicity of chemotherapy

The toxic reaction on PCV of each study were listed in **Table 4**. We focus on the grade 3 or 4 of toxicity. Hematologic toxicity had become the most common symptoms. Gastrointestinal toxicity, neurologic toxicity and allergic skin reactions also happened.

Subgroup analysis

The results suggested that patients come from North America (HR = 0.69, 95% CI 0.54-0.88) will had a longer OS than them come from Europe (HR = 0.88, 95% CI 0.77-1.00) in the RT plus PCV group. The results also suggested that PCV chemotherapy was effective for patients with high-grade glioma (HR = 0.84, 95% CI 0.75-0.95) and was helpless for patients with low-grade glioma (HR = 0.72, 95% CI 0.47-1.10). The results based on the pathology of glioma considered that anaplastic glioma (HR = 0.74, 95% CI 0.63-0.88) was more sensitive for PCV drugs than GBM (HR = 0.92, 95% CI 0.76-1.11). Moreover, there was no significant difference in OS between the two groups in patient with 1p/19q status codeleted or non-codeleted tumors.

The results based on the performance status, age, extent of surgery, RT schedule, isocitrate dehydrogenase (IDH) status, and methyl-guanine-methyl transferase (MGMT) promoter were extracted from the single study. Among these, the results about performance status, age, extent of surgery, and RT schedule were extracted from the study of Medical Research Council Brain Tumor Working Party (MRC), and the relevant results about molecular assessment of IDH and MGMT promoter form the study of van den Bent et al. It seemed that RT schedule, IDH status, and MGMT promoter would affect the efficacy of PCV drugs. Conversely, these extracted data also suggested that performance status, age, and extent of surgery would not affect the OS rate between RT alone group and RT plus PCV group. However, the results of single sample analyses should be treated carefully because of limited data in only one study. The relevant results of pooled analyses and single sample analyses were listed in **Table 5**.

Discussion

Meta-analysis, a quantitative technique to evaluate the clinical effects, is a pooled analysis of series of trials on the same topic. This is the first meta-analysis about RT plus PCV versus RT alone for the treatment of glioma. At the outset of this meta-analysis, there were 4 randomized trials involved 1,584 patients about the effective of RT plus PCV. Our study suggested that PCV chemotherapy was beneficial for

Table 2. Clinical data of randomized controlled trials included in this meta-analysis of radiation therapy plus procarbazine, lomustine and vincristine chemotherapy for glioma (RT versus RT+PCV)

Reference	Treatment	No. of patients	Gender (M/F)	Age (years)	Performance status*	Pathology	Extent of surgery
Medical Research Council Brain Tumor Working Party, 2001	RT	339	227/112	18-70	0-1/ ≥ 2/NA; 245/84/10	Grade 3, AA/grade 4, GBM/other; 60/226/53	None: 1/4; Stereotactic biopsy, biopsy: 81, 55/75, 63; Partial, macroscopic removal: 136, 52/137, 48; NA: 14/8
	RT+PCV	335	223/112	18-70	0-1/ ≥ 2/NA; 238/86/11	Grade 3, AA/grade 4, GBM/other; 53/223/59	
Shaw, 2012	RT	126	NA	40 (22-79)	KPS ≥ 60	Grade 2, astrocytoma: 23%/29%; Grade 2, oligodendroglioma: 45%/40%; Mixed oligoastrocytoma: 32%/31%	Subtotal resection/biopsy; Gross total resection: 9%/11%
	RT+PCV	125	NA	41 (18-82)	KPS ≥ 60		
Cairncross, 2013	RT	143	84/59	43 (19-76)	KPS: 60-70/80-100; 15/128	AO/AOA; 73/70	Total resection: 53/40; Partial procedure: 75/85; Biopsy only: 14/21; No details: 1/2
	RT+PCV	148	90/58	43 (18-75)	KPS: 60-70/80-100; 15/133	AO/AOA; 77/71	
van den Bent, 2013	RT	183	110/73	50 (19-69)	0-1/ ≥ 2; 153/30	AO/AOA/NA; 126/56/1	Biopsy: 25/27; Partial resection: 83/100; Total resection: 75/58
	RT+PCV	185	102/83	49 (19-69)	0-1/ ≥ 2; 155/30	AO/AOA/NA; 139/44/2	

Abbreviations: AA. anaplastic astrocytoma; AO. anaplastic oligodendroglioma; AOA. anaplastic oligoastrocytoma; GBM. glioblastoma multiforme; KPS. Karnofsky performance score; NA. not available. *It means WHO performance status score if there is no special instruction.

Table 3. Summary of adjuvant therapy details

Reference	Delay*	RT details	Chemotherapy (PCV) schedule	Chemotherapy (PCV) details
Medical Research Council Brain Tumor Working Party, 2001	6 weeks	Radiation sites: tumor and margin; 45 Gy in 20 fractions, each of 2.25 Gy over 4 weeks, or 60 Gy in 30 fractions, each of 2 Gy over 6 weeks	3 to 4 weeks after RT	6-week intervals to a maximum of 12 courses; procarbazine 100 mg/m^2 days 1 to 10, lomustine 100 mg/m^2 day 1, and vincristine 1.5 mg/m^2 (max 2 mg) day 1
Shaw, 2012	12 weeks	Radiation sites: tumor and margin; 54 Gy given in 30 fractions of 1.8 Gy each (prescribed to isocenter) over 6 weeks	NA	Six cycles of postradiation procarbazine (60 mg/m^2 orally per day on days 8 through 21 of each cycle), lomustine (110 mg/m^2 orally on day 1 of each cycle), and vincristine (1.4 mg/m^2 [max 2 g]) intravenously on days 8 and 29 of each cycle. The cycle length was 8 weeks
Cairncross, 2013	9 weeks	Radiation sites: tumor and margin; 59.4 Gy in 33 fractions (1.8 Gy each), 5 days a week	Administered before RT	Lomustine 130 mg/m^2 orally on day 1; procarbazine 75 mg/m^2 Orally daily, days 8 through 21; and vincristine 1.4 mg/m^2 intravenously on days 8 and 29. There was no 2-mg limit on vincristine
van den Bent, 2013	6 weeks	Radiation sites: tumor and margin; 45 Gy in 25 daily fractions of 1.8 Gy, 5 fractions aweek. Then, 14.4 Gy in eight fractions of 1.8 Gy, 1 fraction a day, 5 fractions aweek	Within 4 weeks after the end of RT	Lomustine 110 mg/m^2 orally on day 1 with antiemetics, procarbazine 60 mg/m^2 orally on days 8 to 21, and vincristine 1.4 mg/m^2 intravenous on days 8 and 29 (max 2 mg). Cycles were to be repeated every 6 weeks

Abbreviations: NA. not available. *It means maximum delay after surgery.

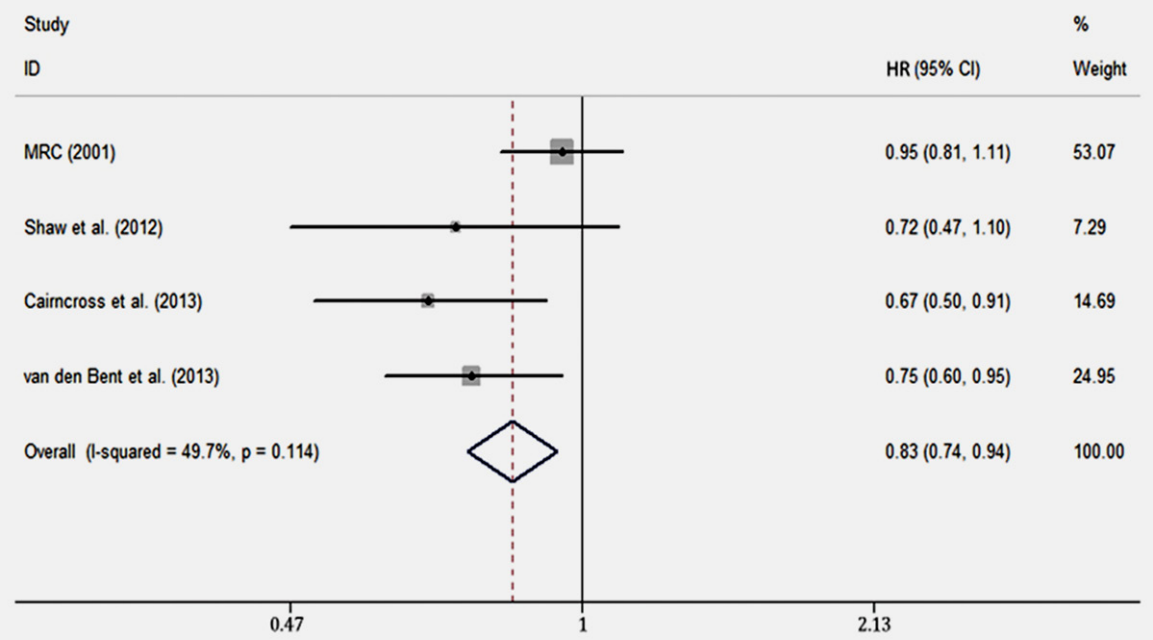

Figure 2. Forest plot for HRs of OS with 4 studies included in this meta-analysis.

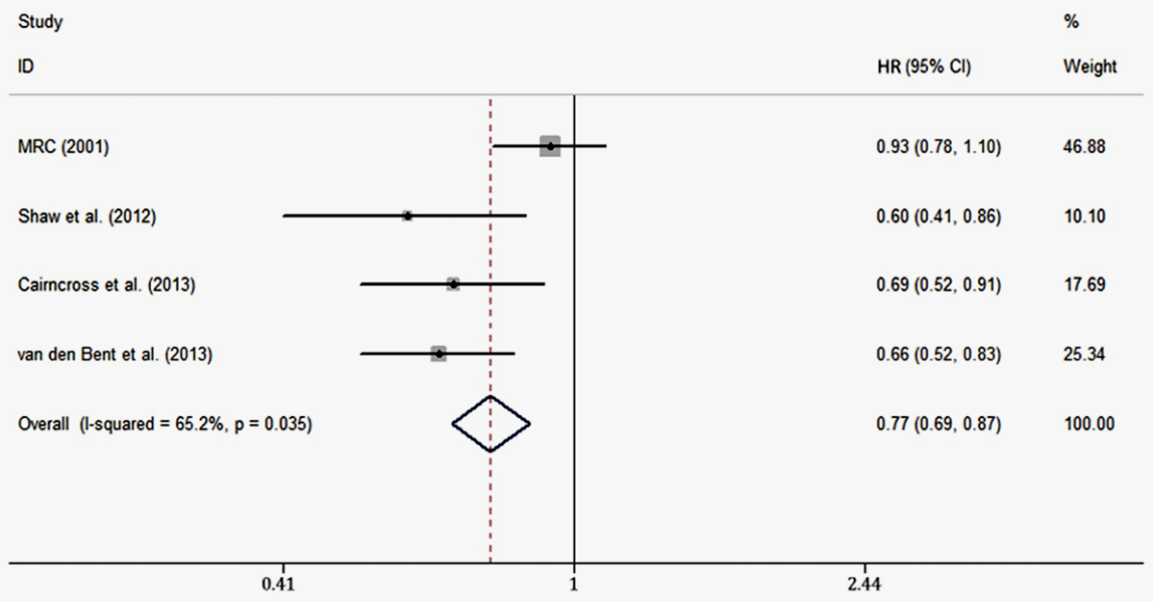

Figure 3. Forest plot for HRs of PFS with 4 studies included in this meta-analysis.

patients with gliomas. Since the early 1990s, chemotherapy with or without radiotherapy had been applied in the treatment of newly diagnosed anaplastic oligodendrogliomas in many centers [17]. Szczepanek et al. considered that the introduction of temozolomide would significant improve the survival rate for newly diagnosed GBM [18]. The results of meta-analysis from Zhang et al. also suggested that adjuvant chemotherapy played a key role in the treatment of anaplastic gliomas [7]. As always, people consider that the blood-brain barrier when talking about the chemotherapy of brain tumor. However, the blood-brain barrier is incomplete or absent within tumor tissue, therefore many polar molecules which do not enter brain tissue have the relatively unrestricted access to enter the intracellular spaces of tumor [19].

Table 4. Toxic reaction on PCV

Reference	Toxicity
Medical Research Council Brain Tumor Working Party, 2001	Grade 3 or 4: hemoglobin (n = 3), WBC count (n = 17), platelets (n = 15), nausea/vomiting (n = 55), neurotoxicity (n = 3), skin rash (n = 1)
Shaw, 2012	Grade 3: hematologic toxicity (RT vs. RT + PCV: 8% vs. 51%); Grade 4: hematologic toxicity (RT vs. RT + PCV: 3% vs. 15%)
Cairncross, 2013	Grade 3 or 4: hematologic (n = 80), neurologic (n = 19), nausea and vomiting (n = 13), hepatic (n = 6), and dermatologic (n = 6)
van den Bent, 2013	Grade 3 or 4: WBC count (n = 48), neutrophils (n = 52), platelets (n = 34), hemoglobin (n = 11), any hematologic toxicity (n = 74), nausea and vomiting (n = 19), polyneuropathy (n = 3), allergic skin reactions (n = 2)

Abbreviations: WBC. White blood cell.

Table 5. Relevant HRs of OS for RT plus PCV versus RT alone on the treatment of glioma

Variables	T/P	HR (95% CI)	I-squared (%)	Z value	*P* value	Model
Pooled analyses						
Overall	4/1,584	0.83 (0.74, 0.94)	49.7	3.10	0.002	Random effect
Country						
North America	2/542	0.69 (0.54, 0.88)	0.0	3.02	0.003	Fixed effect
Europe	2/1,042	0.88 (0.77, 1.00)	63.8	1.91	0.056	Random effect
Tumor grade						
Low-grade glioma	1/251	0.72 (0.47, 1.10)	NA	1.51	0.130	NA
High-grade glioma	3/1,333	0.84 (0.75, 0.95)	63.4	2.80	0.005	Random effect
Pathology						
Anaplastic glioma	3/772	0.74 (0.63, 0.88)	0.0	3.53	< 0.001	Fixed effect
GBM	1/449	0.92 (0.76, 1.11)	NA	0.86	0.39	NA
1p/19q stauts						
Codeleted	2/206	0.58 (0.40, 0.84)	0.0	2.89	0.004	Fixed effect
Noncodeleted	2/NA	0.45 (0.32, 0.64)	0.0	4.52	0.000	Fixed effect
Single sample analyses						
Performance status						
0-1	1/487	0.97 (0.80, 1.17)	NA	0.33	0.74	NA
2	1/138	0.93 (0.65, 1.33)	NA	0.41	0.68	NA
3-4	1/32	1.58 (0.63, 3.95)	NA	0.98	0.33	NA
Age						
< 45	1/159	1.00 (0.69, 1.46)	NA	0.02	0.98	NA
45-60	1/365	0.96 (0.77, 1.20)	NA	0.34	0.74	NA
> 60	1/150	0.79 (0.57, 1.11)	NA	1.36	0.17	NA
Extent of surgery						
Biopsy	1/281	0.94 (0.74, 1.20)	NA	0.48	0.63	NA
Partial resection	1/274	1.06 (0.83, 1.35)	NA	0.44	0.66	NA
Complete resection	1/100	0.67 (0.44, 1.02)	NA	1.85	0.06	NA
RT schedule						
45 Gy	1/135	0.57 (0.39, 0.82)	NA	3.04	0.002	NA
55 Gy	1/38	1.28 (0.66, 2.47)	NA	0.72	0.47	NA
60 Gy	1/501	1.05 (0.87, 1.26)	NA	0.53	0.60	NA
IDH status						
Mutated	1/81	0.53 (0.30, 0.95)	NA	NA	NA	NA
Wild type	1/97	0.78 (0.52, 1.18)	NA	NA	NA	NA
MGMT promoter						
Methylated	1/136	0.65 (0.43, 0.98)	NA	NA	NA	NA
Unbmethylated	1/47	0.81 (0.44, 1.49)	NA	NA	NA	NA

Abbreviations: GBM. glioblastoma multiforme; IDH. isocitrate dehydrogenase; MGMT. methyl-guaninemethyl transferase; NA. not available; T/P. No. of trials/No. of patients.

In particular, the characteristics of patients and grade of tumors may affect the efficacy of chemotherapy. The subgroup analysis indicated that PCV did not prolong the OS for the patients with low-grade gliomas. Kim et al. also suggested that PCV therapy provided durable response for patients with grade 3 or 4 oligoastrocytomas [20]. People of difference races may be also affect the results of chemotherapy. This meta-analysis suggested that Europeans were more sensitive to chemotherapy than people come from North America. Many studies considered that codeletion of chromosomes 1p/19q, a predictive and prognostic biomarker, indicated the tumor that grows slowly and sensitivity to chemotherapy [1, 8, 21]. Zhao et al. considered that the codeletion of 1p/19q was associated with better survival rates in patients with glioma, but the effect of isodeletion of 1p or 19q might be less extent and marginal. In this meta-analysis, the results suggested that the codeletion of 1p/19q had a similar OS and PFS compared with the patients with noncodeletion of 1p/19q [22]. The different RT schedule may also affect the survival results. The study from MRC indicated that OS of 45 Gy was significantly greater than it in those planned for 60 Gy [12]. The meta-analysis of Fine et al. speculated that efficacy of chemotherapy would be greatest in patients who had received the most suitable dose, because these patients had the least tumor burden on commencing chemotherapy [23]. The efficacy may be associated with the long-term survival. Shaw et al. considered that the survival curves separated significantly after 2 years, with both OS and PFS favoring patients treated with RT plus PCV [11]. The results of study from Tsitlakidis et al. suggested that cytoreductive was associated with better overall survival than biopsy for patients with supratentorial malignant glioma [24]. In fact, many more factors such as performance status, surgical resection, performance status, age, molecular status and so on, may affecting the OS, that should attract our attentions.

RT plus PCV had a longer OS and PFS than RT alone group for the treatment of patients with gliomas. However, we should also take into account the economic burden and side effects which chemotherapy brought to patients. There is no doubt that adjuvant chemotherapy will increase economic burden on patients. Furthermore, we must pay attention to the toxic reaction on PCV chemotherapy. Martin et al. considered that the major impact of PCV on health-related quality of life was nausea/vomiting, loss of appetite, and drowsiness and shortly after treatment [25, 26]. There was no long-term impact on patients with PCV chemotherapy. The related information of toxicity from 4 trials listed in **Table 4** showed that myelosuppression was the most dangerous factor for the patients.

The main advantages embodied in our meta-analysis were: Firstly, our meta-analysis was the first report on comparing RT plus PCV versus RT alone for the treatment of glioma patients after surgery. Our study suggested that RT plus PCV is better than RT alone; Secondly, we also checked the influence of the characteristics of patients and study design on the results of clinical therapy.

However, there were some possible limitations on the results of meta-analysis. Firstly, the 4 RCTs included in this meta-analysis were only involved with 1,584 patients and designed in the western developed countries; Secondly, different types of glioma may be have different sensitivity to the PCV chemotherapy; Thirdly, the results of this meta-analysis should be treated with caution because of the heterogeneity among study designs. The source of the heterogeneity may be due to the difference in the ethnic groups, the pathological characteristic of tumor and so on. Next, we still need a large sample of RCTs to verify the efficacy of PCV chemotherapy. At the same time, the different characteristics of patients and tumors will produce what kind of impact on the PCV chemotherapy.

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Disclosure of conflict of interest

None.

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