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Review Article

Radiotherapy plus chemotherapy in the treatment of malignant glioma: a systematic review and meta-analysis

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Abstract: Radiotherapy (RT) plus adjuvant chemotherapy has been exploring the effectiveness in the treatment of malignant gliomas compared with RT alone, but have shown inconsistent results. Hence, we performed a meta-analysis to compare the efficacy of RT plus adjuvant chemotherapy with RT alone in patients with malignant gliomas after surgery. PubMed, EMBASE, and the Cochrane Library were searched for randomized controlled trials published in English, which investigating the efficacy of RT plus adjuvant chemotherapy versus RT alone for malignant glioma patients. The evaluation indices of clinical outcomes included hazard ratios (HRs) of overall survival (OS) and progression-free survival (PFS). Individual HR with 95% confidence intervals were pooled and analyzed. Twenty-two studies involving 5,021 patients satisfied our inclusion criteria. The pooled results of RCTs demonstrated that RT plus adjuvant chemotherapy will have a longer OS (HR = 0.78, 95% CI 0.71-0.85) and a longer PFS (HR = 0.69, 95% CI 0.60-0.79) than RT alone in the treatment of malignant gliomas. Our results of meta-analysis suggested that RT plus chemotherapy prolonged the OS and PFS rate compared with RT alone in the treatment of malignant gliomas. In future research, it is necessary for subgroup analyses of variables such as histology, extent of surgery, or performance status to be conducted to confirm these findings.

Keywords: Chemotherapy, malignant glioma, meta-analysis, radiotherapy

Introduction

Glioma is the most common intracranial tumor, which accounts for about 40% of intracranial tumors and the annual incidence rate is about 3-8 cases per 100,000 population worldwide [1]. Malignant gliomas are among the most threatening of cancers to human health, which are also difficult to diagnose and challenging to treat [2]. Clinical practice shows that radical surgery and radiotherapy (RT) will prolong the expected median survival for patients with malignant glioma [3]. Nevertheless, despite surgery and RT, patients with malignant glioma recur largely at the primary lesion with few long-term survivors. As the presence of the blood-brain barrier and the toxicity of chemotherapy drugs exist, the safety and efficacy of addition of chemotherapy remains controversial [4]. There have been many trials to investigate the effective of adjuvant chemotherapy. However, these studies are difficult to get a convincing conclusion because of the limitation of sample size and heterogeneity of research design. Hidebrand et al. considered that combination of RT and chemotherapy could not improve the overall survival (OS) rate of glioma patients [5]. However, conflicting results have been reported that RT plus chemotherapy increase the OS rate for patients with glioblastoma than RT alone [6]. A meta-analysis from glioma meta-analysis trialists (GMT) group had reported that chemotherapy had a small but clear improvement in survival for patients with high-grade glioma, which encouraged further study of drug treatment for these tumors in clinic [7]. However, the included studies in this meta-analysis were a little long way from us and the data volume was limited. Recently, Zhang et al. also conducted a meta-analysis to answer whether patients with anaplastic glioma who were treated with RT plus chemotherapy will

increase OS and progression-free survival (PFS) compared with who treated with RT alone [8]. The results suggested that chemotherapy play a beneficial role in the treatment of anaplastic gliomas, but the efficacy of adjuvant chemotherapy still needed further investigation in the treatment of anaplastic astrocytoma.

Several randomized controlled trials (RCTs) were newly conducted to detect the efficacy and safety of RT plus chemotherapy in treatment of malignant gliomas [9-12]. Herein, we performed a meta-analysis to compare RT plus chemotherapy with RT alone in the treatment of malignant gliomas. Moreover, we also conducted a series of subgroup analysis to evaluate the effect of the heterogeneity of research design and different kinds of chemotherapy drugs on treatment outcomes.

Material and methods

Study selection

Two independent reviewers carried out a comprehensive search of PubMed/Cochrane libraries and EMBASE for relevant RCTs published up to December 1, 2015. The search terms with MeSH heading included: “glioma”, “chemotherapy” and “radiotherapy”. The search process was limited to English language and human subjects. In addition, we also checked the reference lists of identified articles to search the eligible trials. This process were carried out iteratively until no other potentially articles could be founded. If a discrepancy was found between the 2 reviewers’ assessments, it was resolved by group discussion.

Inclusion and exclusion criteria

The RCTs included in this meta-analysis satisfying the following criteria: (i) all patients with malignant glioma who had undergone surgery; (ii) adjuvant chemotherapy plus RT compared with RT after surgery; (iii) chemotherapy and RT were specifically defined; (iv) related data of the OS or PFS were available. The exclusion criteria included: (i) conference abstracts, reviews, letters, systematic reviews and case reports; (ii) metastatic and recurrent glioma after surgical resection; (iii) studies lacking relevant outcome data. If any data were duplicated or shared among studies, the published in the latest or more detailed study was used.

Data extraction and quality assessment

Two independent authors (Chen and Huang) extracted the relevant data. The extracted data included study characteristics (treatment, number of patients, gender, age, performance status, and median follow-up year), report characteristics (year, country, and study period), specific radiotherapy and chemotherapy details (pathology, RT details, chemotherapy schedule, and chemotherapy details), the toxic reaction on chemotherapy drugs, and relevant outcome data (the hazard ratios (HRs) value of OS and PFS). Any disagreements were resolved by group discussion.

We used the Jadad scale to assess the methodologic quality of each study included. The main scale consists of 5 items: randomization (0-1 points), double-blind (0-1 points) reporting, a description of the randomization methods (0-1 points), allocation concealment (0-1 points), and follow-up reporting (0-1 points). The quality scale ranged from 0 to 5 points. Higher scores meant better reporting. The studies were classified as low quality if the Jadad score was ≤ 3 and high quality if the score was ≥ 4.

Subgroup analysis

Subgroup analysis was applied based on the study design (i.e., Jadad score, sample size, publication date) and characteristics of patients (i.e., pathology, dose of radiation, age, molecular assessment, extent of surgery, and chemotherapy drugs).

Data analysis

The results of our study were described using statistics of HRs and 95% confidence intervals (CIs). Statistical significance was found at 2-tailed P less than .05. The I^2 statistic was used to assess the statistical heterogeneity. I^2 more than 50% with P less than .10 was considered as significant heterogeneity across studies. HRs of individual trials and overall were displayed in forest plots. We used random effect to calculate the combined HR with its 95% CI if the heterogeneity is significant, otherwise we would use the fixed effect. Sensitivity analysis was applied to estimate the contribution of each trial to the meta-analysis by exclusion of individual studies one at a time and

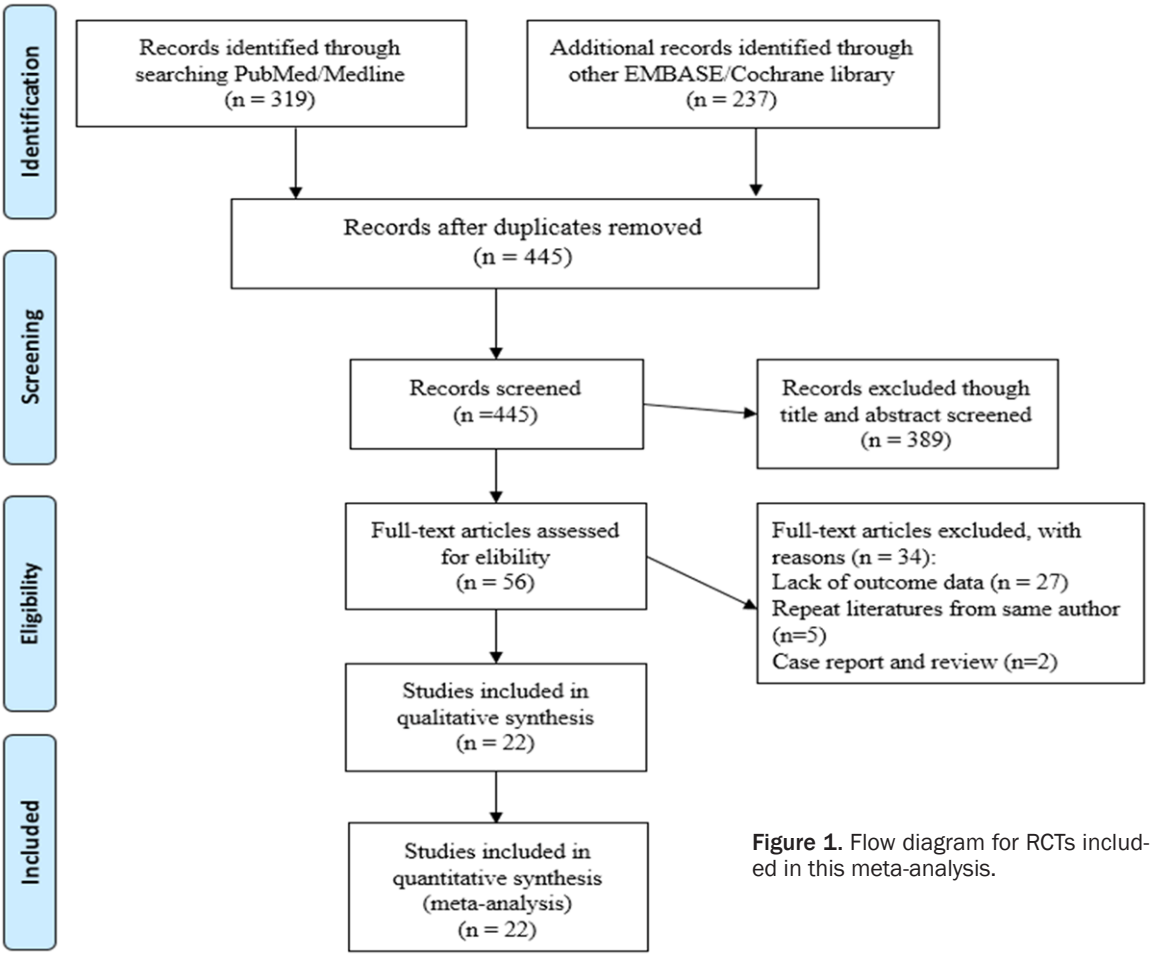

Figure 1. Flow diagram for RCTs included in this meta-analysis.

then recalculation of the pooled HR and its 95% CI for the remaining studies. We used Begg's funnel plot and Egger's test to assess the publication bias graphically and statistically.

Results

Study identification and characteristics

The trial flow is shown in **Figure 1**. Twenty-two RCTs were ultimate included in the meta-analysis, which included 5,021 patients with a diagnosis of malignant glioma [5, 6, 9-28]. The studies were conducted in 14 countries. The sample size of the RCT ranged from 20 to 674. Among the 22 studies included here, different drugs such as carmustine (BCNU), lomustine (CCNU), dibromodulcitol, dacarbazine, procarbazine, and temozolomide (TMZ) had been used in the treatment of chemotherapy for patients with malignant glioma. As the study characteristics and the patients' demographic information are highlighted in **Table 1**, and the details of RT and adjuvant chemotherapy are listed in **Table 2**.

Meta-analysis

All the 22 trials included in the analysis reported the HR of OS rate. The results showed that RT plus adjuvant chemotherapy will prolong the OS rate compared with RT alone (HR = 0.78, 95% CI [0.71-0.85]). Forest plot for HRs of OS was shown in **Figure 2**. Fourteen of the 22 trials included in the analysis reported the HR of PFS rate. The results of meta-analysis suggested that RT plus adjuvant chemotherapy group has a better PFS rate than the RT alone group (HR = 0.69, 95% CI [0.60-0.79]) **Figure 3**.

Toxicity of chemotherapy drugs

The toxic reaction on chemotherapy drugs of each study included in this meta-analysis were listed in **Table 3**. Hematologic toxicity, gastroin-

Table 1. Clinical data and Jadad score of each RCT included in this meta-analysis

Author	Year	Country	Study period	Treatment	No. of patients	Gender (M/F)	Age (years)	Performance status*	Median follow-up year	Jadad score
Weir	1976	Poland	1971-1973	RT	10	NA	NA	NA	NA	3
				RT + CCNU	10	NA	NA	NA		
Walker	1978	United States	1969-1972	RT	93	58/35	56 (28-78)	NA	NA	3
				RT + BCNU	100	75/25	57 (6-78)	NA		
Solero	1979	Italy	1972-1976	RT	33	NA	NA	NA	NA	3
				RT + BCNU/CCNU	72	NA	NA	NA		
Walker	1980	United States	1972-1975	RT	117	NA	NA	Median KPS: 60	NA	3
				RT + BCNU/CCNU	238	NA	NA	Median KPS: 65		
EORTC	1981	Belgium	NA	RT	55	27/28	≤ 50/> 50; 22/33	NA	1.12	4
				RT + CCNU	61	37/24	≤ 50/> 50; 23/38	NA		
Afra	1983	Hungary	1978-1981	RT	32	21/11	NA	KPS: 60-69/> 70; 4/27	NA	4
				RT + DBD/CCNU	59	30/29	NA	KPS: 60-69/> 70; 6/48		
Chang	1983	United States	1974-1979	RT	167	110/57	NA	≤ 80/> 80; 90/77	NA	3
				RT + BCNU/CCNU/DTIC	344	205/139	NA	KPS: ≤ 80/> 80; 193/151		
Green	1983	United States	NA	RT	156	NA	NA	NA	NA	3
				RT + BCNU/PCZ	153	NA	NA	NA		
Trojanowski	1988	Poland	NA	RT	54	NA	NA	NA	NA	4
				RT + CCNU	71	NA	NA	NA		
Hildebrand	1994	Belgium	1989-1991	RT	135	76/59	54 (19-79)	Median KPS: 80	NA	4
				RT + BCNU/DBD	135	63/72	54 (20-75)	Median KPS: 80		
MRC	2002	United Kingdom	1988-1997	RT	339	227/112	18-70	0-1/≥ 2/NA; 245/84/10	3 (1-8)	4
				RT + PCV	335	223/112	18-70	0-1/≥ 2/NA; 238/86/11		
Athanassiou	2005	Greece	2000-2002	RT	53	34/19	≤ 50/> 50; 11/42	KPS: ≤ 80/> 80; 36/17	0.93 (0.28-2.25)	3
				RT + TMZ	57	36/21	≤ 50/> 50; 9/48	KPS: ≤ 80/> 80; 30/27		
Henriksson	2006	Sweden	NA	RT	63	42/21	53.3 (25-84)	0-2	5.2-8.0	4
				RT + estramustine	59	35/24	55.7 (22-86)	0-2		
Levin	2006	United States and Canada	1996-1999	RT	79	57/22	58 (25-79)	KPS: 60-70/80-100; 16/63	NA	5
				RT + marimastat	83	51/32	57 (21-77)	KPS: 60-70/80-100; 16/67		
Hildebrand	2008	Belgium	1994-2000	RT	94	53/41	40 (19-79)	0-1/≥ 2; 76/18	NA	4
				RT + DBD/BCNU	87	51/36	44 (24-74)	0-1/≥ 2/NA; 65/16/6		
Kocher	2008	Germany	2002-2004	RT	33	26/7	58 (37-69)	0-1/2; 31/2	3.0	4
				RT + TMZ	29	15/14	59 (34-67)	0-1/2; 29/0		
Stupp	2009	Switzerland	2000-2002	RT	286	175/111	57 (23-71)	0/1/2; 110/141/35	2.34	4
				RT + TMZ	287	185/102	56 (19-70)	0/1/2; 113/136/38		
Shaw	2012	United States	1998-2002	RT	126	NA	40 (22-79)	KPS ≥ 60	5.9	3
				RT + PCV	125	NA	41 (18-82)	KPS ≥ 60		
Cairncross	2013	Canada	1994-2002	RT	143	84/59	43 (19-76)	KPS: 60-70/80-100; 15/128	11.3 (0.5-16.8)	4
				RT + PCV	148	90/58	43 (18-75)	KPS: 60-70/80-100; 15/133		
Solomon	2013	Cuba	NA	RT	38	19/19	≤ 50/> 50; 21/17	KPS: 60-70/80-100; 15/23	NA	5
				RT + nimotuzumab	32	21/11	≤ 50/> 50; 19/13	KPS: 60-70/80-100; 5/27		
Tham	2013	Singapore	2000-2010	RT	26	13/13	≤ 65/> 65; 21/5	KPS: ≤ 80/> 80; 20/6	1.7	3
				RT + TMZ	36	21/15	≤ 65/> 65; 34/2	KPS: ≤ 80/> 80; 18/18		
Van den Bent	2013	Netherlands	1995-2002	RT	183	110/73	50 (19-69)	0-1/≥ 2; 153/30	11.7	4
				RT + PCV	185	102/83	49 (19-69)	0-1/≥ 2; 155/30		

BCNU: carmustine; *CCNU:* lomustine; *DBD:* dibromodulcitol; *DTIC:* dacarbazine; *KPS:* Karnofsky performance score; *M/F:* male/female; *NA:* not available; *PCZ:* procarbazine; *PCV:* carmustine, lomustine and procarbazine; *RT:* radiotherapy; *TMZ:* temozolomide; *It means WHO performance status score if there is no special instruction.

Table 2. Summary of RT and adjuvant chemotherapy therapy details

Reference	Pathology	RT details	Chemotherapy Schedule	Chemotherapy details
Weir, 1976	astrocytoma	40 to 45 Gy; 25 fractions; 4-5 weeks;	coincided with the first day of RT	CCNU 130 mg/m^2 orally, every 6 weeks
Walker, 1978	anaplastic glioma	50 to 60 Gy, 30-35 fractions; 6-7 weeks	NA	BCNU 80 mg/m^2 * 3; intravenously, every 6-8 weeks
Solero, 1979	GBM	50 Gy; 25-30 fractions; 5 weeks	started along with RT	BCNU 80 mg/m^2 * 3 intravenously, every 6-8 weeks; CCNU 130 mg/m^2 orally, every 6-8 weeks
Walker, 1980	GBM, anaplastic astrocytoma	60 Gy; 30-35 fractions; 6-7 weeks;	during the first RT	Methyl lomustine 220 mg/m^2 orally, every 6-8 weeks; carmustine 80 mg/m^2 * 3 intravenously, every 6-8 weeks
EORTC, 1981	GBM, astrocytoma, oligodendroblastoma	55-60 Gy; 30 fractions; 6 weeks;	coincided with the first day of RT	CCNU 130 mg/m^2 orally; epipodophyllotoxin 60 mg/m^2 intravenously, every 6 weeks
Afra, 1983	glioblastoma; malignant astrocytoma	51 Gy; 25-30 fractions; 5-6 weeks;	during the first RT	DBD a single dose of 400 mg/sq m every 5th day, for a total of six to eight doses; CCNU in a single dose of 80 to 100 mg/sq m on Day 1;
Chang, 1983	astrocytoma	60 Gy; 35 fractions; 7 weeks;	started on day one of radiotherapy	BCNU 80 mg/m^2 * 3 intravenously, every 6-8 weeks; CCNU 125 mg/m^2 orally, every 8 weeks; DTIC 150 mg/m^2 * 5 intravenously, every 4 weeks
Green, 1983	NA	60 Gy; 30-35 fractions; 6-7 weeks	NA	BCNU 80 mg/m^2 * 3 intravenously, every 8 weeks; PCZ 150 mg/m^2 * 28 days, every 8 weeks
Trojanowsk, 1988	astrocytoma, oligodendroglioma	60 Gy; 30 fractions; 6 weeks;	started along with RT	CCNU 100 mg/m^2 orally, every 6-8 weeks
Hildebrand, 1994	anaplastic astrocytoma, glioblastoma	60 Gy; 30-35 fractions; 6-7 weeks;	during the first year following radiation therapy	DBD 700 mg/m^2 * 6 orally during radiotherapy, BCNU 150 mg/m^2 intravenously; DBD 1000 mg/m^2 orally every 6 weeks
MRC, 2001	anaplastic astrocytoma, GBM	45 Gy in 20 fractions, each of 2.25 Gy over 4 weeks	3 to 4 weeks after RT	PCZ 100 mg/m^2 days 1 to 10, CCNU 100 mg/m^2 day 1, and vincristine 1.5 mg/m^2 (max 2 mg) day 1
Athanassiou, 2005	GBM	45 Gy in 20 fractions, each of 2.25 Gy over 4 weeks	3 to 4 weeks after RT	6 cycles of adjuvant TMZ (150 mg/m^2 of TMZ on days 1 through 5 and 15 to 19 every 28 days)
Henriksson, 2006	astrocytoma	60 Gy in 30 daily fractions of 2.0 Gy, 5 days a week	four weeks after RT	estramustine phosphate, 280 mg * 2 daily from the day of diagnosis
Levin, 2006	GBM	56 Gy in 28 daily fractions of 2.0 Gy, 5 times a week	from the day of diagnosis, during radiotherapy	marimastat at 10 mg orally twice daily
Hildebrand, 2008	anaplastic astrocytoma	60 Gy delivered in 30-33 fractions	until study termination	DBD 1000 mg/m^2 on day 1, and BCNU 130 mg/m^2 on day 2, given every six weeks
Kocher, 2008	glioblastoma	60 Gy in 2.0 Gy daily fractions, 5 fractions per week	before each radiotherapy fraction	a single daily oral dose of 75 mg/m^2 1-2 hours
Stupp, 2009	GBM, anaplastic astrocytoma, other	60 Gy in daily fractions of 1.8-2.0 Gy	during RT	TMZ at a daily dose of 75 mg/m^2 given 7 days per week from the first to the last day of radiotherapy. After a 4-week break, six cycles of adjuvant oral TMZ (150-200 mg/m^2) for 5 days every 28 days.
Shaw et al, 2012	astrocytoma, oligodendroglioma, Mixed oligoastrocytoma	60 Gy in 30 daily fractions of 2 Gy each	concomitant RT	6 cycles of postradiation PCZ (60 mg/m^2 orally per day on days 8 through 21 of each cycle), CCNU (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	anaplastic oligodendroglioma, anaplastic oligoastrocytoma	54 Gy given in 30 fractions of 1.8 Gy each (prescribed to isocenter) over 6 weeks	NA	CCNU 130 mg/m^2 orally on day 1; PCZ 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
Solomon, 2013	anaplastic astrocytoma, GBM	59.4 Gy in 33 fractions (1.8 Gy each), 5 days a week	administered before RT	200 mg of nimotuzumab, intravenously infused over 30 to 60 minutes.
Tham, 2013	anaplastic glioma	a total dose of 50 to 60 Gy	during the radiation period	6 months of TMZ at 150 to 200 mg/m^2, given for 5 of every 28 days
van den Bent, 2013	anaplastic oligodendroglioma, anaplastic oligoastrocytoma, other	a total dose of 50 to 60 Gy, 5 days per week	concurrently with RT	CCNU 110 mg/m^2 orally on day 1 with antiemetics, PCZ 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

BCNU: carmustine; *CCNU:* lomustine; *DBD:* dibromodulcitol; *DTIC:* dacarbazine; *GBM:* glioblastoma multiforme; *NA:* not available; *PCZ:* procarbazine; *PCV:* carmustine, lomustine and procarbazine; *RT:* radiotherapy; *TMZ:* temozolomide.

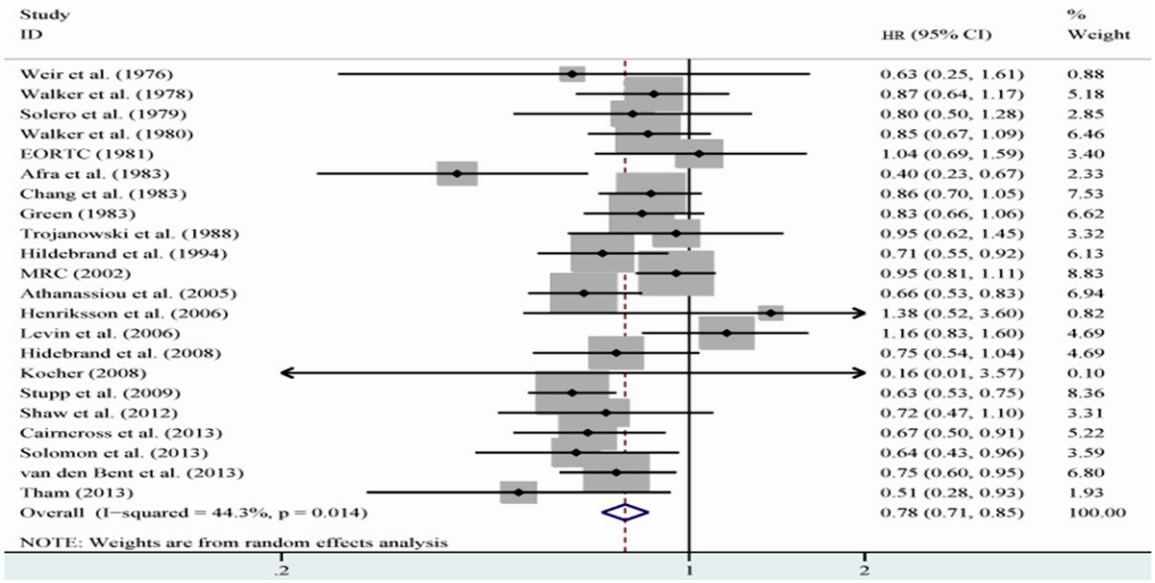

Figure 2. Forest plot for HRs of OS with 22 studies included in this meta-analysis.

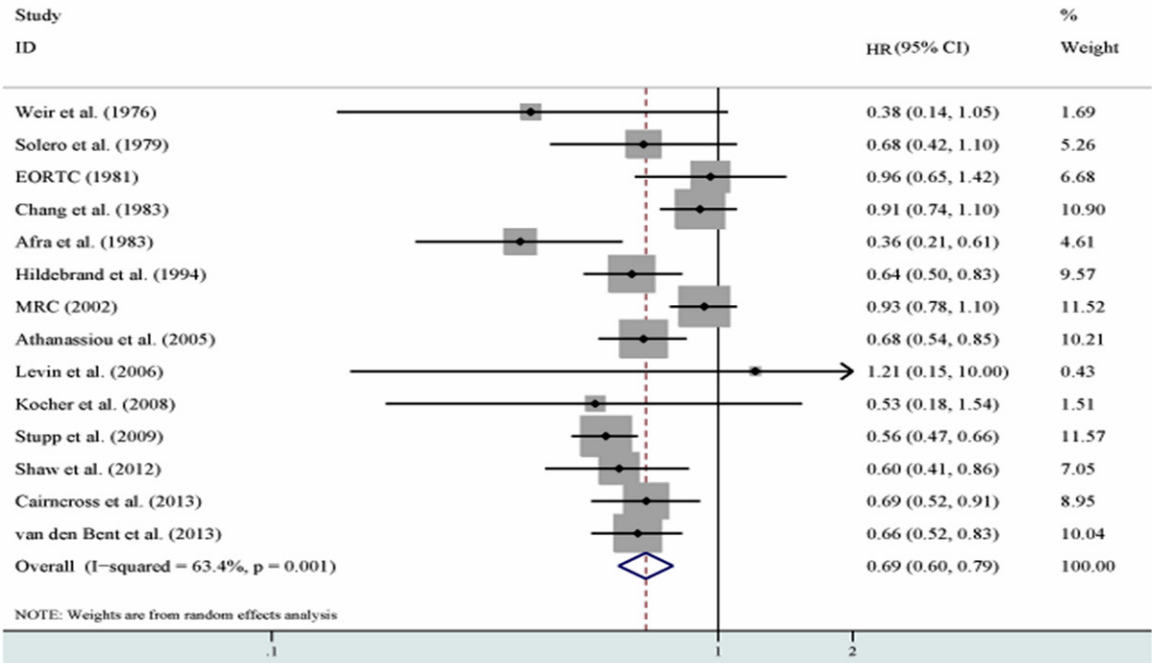

Figure 3. Forest plot for HRs of PFS with 14 studies included in this meta-analysis.

testinal toxicity, and neurologic toxicity, and allergic skin reactions were the most common symptoms.

Subgroup analysis based on study design

In the first instance, we introduced 2005 year as a divide to distinguish the "publication date (year ≥ 2005 and year < 2005)". The results suggested that in both the publication date year ≥ 2005 (HR = 0.70, 95% CI [0.64-0.77]) and year < 2005 (HR = 0.85, 95% CI [0.78-0.93]) groups OS rate was significantly higher in RT plus chemotherapy group than RT alone group. Moreover, the results of subgroup meta-analysis in high quality trials (Jadad score ≥ 4) and large scale trials (number > 100) groups were consistent with the overall result. The application of chemotherapy was effective in

Table 3. Toxic reaction on chemotherapy drugs

Reference	Chemotherapy drugs	Chemotherapy toxicity
Weir, 1976	CCNU	NA
Walker, 1978	BCNU	platelet count (n = 21), WBC count (n = 88)
Solero, 1979	BCNU/CCNU	NA
Walker, 1980	BCNU/CCNU	NA
EORTC, 1981	CCNU	NA
Afra, 1983	DBD/CCNU	platelet count (n = 12), WBC count (n = 8)
Chang, 1983	BCNU/CCNU/DTIC	platelet count (n = 7), WBC count (n = 7)
Green, 1983	BCNU/PCZ	NA
Trojanowsk, 1988	CCNU	NA
Hildebrand, 1994	BCNU/DBD	WBC count (n = 22), granulocytes (n = 14), platelets (n = 23), hemoglobin (n = 5)
MRC, 2002	PCV	hemoglobin (n = 3), WBC count (n = 17), platelets (n = 15), nausea/vomiting (n = 55), neurotoxicity (n = 3), skin rash (n = 1)
Athanassiou, 2005	TMZ	leukopenia (n = 2); thrombocytopenia (n = 3); myelotoxicity (n = 1)
Henriksson, 2006	Estramustine	seizures (n = 9), nausea/vomiting (n = 28), pneumonia (n = 4), diarrhoea (n = 4), hypothyreosis (n = 3), vaginal bleeding (n = 6)
Levin, 2006	MT	musculoskeletal toxicities (n = 29)
Hildebrand, 2008	DBD/BCNU	nausea/vomiting (n = 5)
Kocher, 2008	TMZ	nausea (n = 4), lymphopenia (n = 33)
Stupp, 2009	TMZ	haematotoxicity (n = 7), non-haematotoxicity (n = 10), and both toxicities (n = 2)
Shaw et al, 2012	PCV	hematologic toxicity (RT vs. RT + PCV: 8% vs. 51%); hematologic toxicity (RT vs. RT + PCV: 3% vs. 15%)
Cairncross, 2013	PCV	hematologic (n = 80), neurologic (n = 19), nausea and vomiting (n = 13), hepatic (n = 6), and dermatologic (n = 6)
Solomon, 2013	Nimotuzumab	headache (n = 17), seizures (n = 6), dry radiodermitis (n = 5), asthenia (n = 4), liver function tests alterations (n = 5), and alopecia (n = 7)
Tham, 2013	TMZ	NA
van den Bent, 2013	PCV	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)

Note: BCNU: carmustine; CCNU: lomustine; DBD: dibromodulcitol; DTIC: dacarbazine; GBM: glioblastoma multiforme; MT: marimastat; NA: not available; PCZ: procarbazine; PCV: carmustine, lomustine and procarbazine; RT: radiotherapy; TMZ: temozolomide; WBC: white blood cell.

Table 4. The listed results of sensitivity analyses based on design of studies for OS

Outcome	n (N)	HR (95% CI)	Z Value	*P* Value	I^2 (%)	*P* Value of Heterogeneity	Model
All included trials	22 (5021)	0.78 (0.71, 0.85)	5.44	< 0.001	44.3	0.014	Random effect
High quality trials (Jadad score ≥ 4)	13 (3105)	0.78 (0.68, 0.90)	3.45	0.001	55.7	0.007	Random effect
Large scale trials (number > 100)	17 (4716)	0.80 (0.74, 0.88)	4.88	< 0.001	40.6	0.042	Random effect
Publication date (year ≥ 2005)	11 (2252)	0.70 (0.64, 0.77)	7.44	< 0.001	35.5	0.115	Fixed effect
Publication date (year < 2005)	11 (2769)	0.85 (0.78, 0.93)	3.78	< 0.001	23.8	0.217	Fixed effect
Region							
Europe	13 (2817)	0.75 (0.66, 0.86)	4.11	< 0.001	53.0	0.026	Random effect
North America	7 (2072)	0.84 (0.76, 0.94)	3.23	0.001	8.0	0.367	Fixed effect
South America	1 (70)	0.64 (0.43, 0.96)	2.18	0.029	NA	NA	NA
Asia	1 (62)	0.51 (0.28, 0.93)	2.20	0.028	NA	NA	NA

HR: hazard ratio.

Table 5. The listed results of subgroup analyses based on characteristics of patients for OS

Variables	n (N)	HR (95% CI)	Z Value	*P* Value	I^2 (%)	*P* Value of Heterogeneity	Model
All included trials	22 (5021)	0.78 (0.71, 0.85)	5.44	< 0.001	44.3	0.014	Random effect
Pathology							
Anaplastic glioma	3 (436)	0.77 (0.62, 0.95)	2.48	0.013	18.8	0.292	Fixed effect
Astrocytoma	3 (653)	0.86 (0.71, 1.05)	1.47	0.142	0.0	0.511	Fixed effect
GBM	3 (377)	0.84 (0.58, 1.22)	0.91	0.365	74.1	0.021	Random effect
Dose of radiation							
< 60 Gy	12 (2262)	0.77 (0.66, 0.89)	3.51	< 0.001	57.4	0.007	Random effect
≥ 60 Gy	10 (2759)	0.76 (0.70, 0.83)	4.91	< 0.001	19.6	0.263	Fixed effect
Age							
Age < 50	1 (183)	0.6 (0.4, 0.8)	NA	NA	NA	NA	NA
Age ≥ 50	1 (390)	0.7 (0.5, 0.8)	NA	NA	NA	NA	NA
Molecular assessment							
1p/19q status noncodeleted	2/206	0.45 (0.32, 0.64)	4.52	< 0.001	0.0	0.938	Fixed effect
1p/19q status codeleted	2/206	0.58 (0.40, 0.84)	2.89	< 0.001	0.0	0.943	Fixed effect
MGMT unmethylated	1 (573)	0.6 (0.4, 0.8)	NA	NA	NA	NA	NA
MGMT methylated	1 (573)	0.3 (0.2, 0.4)	NA	NA	NA	NA	NA
Extent of surgery							
Biopsy	2 (117)	0.79 (0.55, 1.12)	1.32	0.188	45.9	0.174	Fixed effect
Partial resection	2 (329)	0.91 (0.38, 2.15)	0.22	0.828	90.5	0.001	Random effect
Complete resection	2 (289)	0.65 (0.48, 0.87)	2.92	0.004	0.0	0.426	Fixed effect
Chemotherapy drugs							
BCNU/CCNU	6 (914)	0.88 (0.76, 1.02)	1.72	0.085	0.0	0.916	Fixed effect
TMZ	4 (807)	0.63 (0.55, 0.72)	6.73	< 0.001	0.0	0.688	Fixed effect
PCV	4 (1584)	0.83 (0.74, 0.94)	3.10	0.002	49.7	0.114	Fixed effect

BCNU: carmustine; *CCNU:* lomustine; *HR:* hazard ratio; *KPS:* Karnofsky performance status; *PCV:* carmustine lomustine and procarbazine; *TMZ:* temozolomide.

almost all world regions. The relevant results were listed in **Table 4**.

Subgroup analyses based on characteristics of patients

The results of subgroup analyses based on the pathology of malignant glioma suggested that the chemotherapy drugs was effective for patients with anaplastic glioma (HR = 0.77, 95% CI [0.62-0.95]) and was helpless for patients with astrocytoma (HR = 0.86, 95% CI [0.71-1.05]) and glioblastoma multiforme (GBM) (HR = 0.84, 95% CI [0.58-1.22]). The results also considered that dose of radiation, age, extent of surgery, and molecular assess-

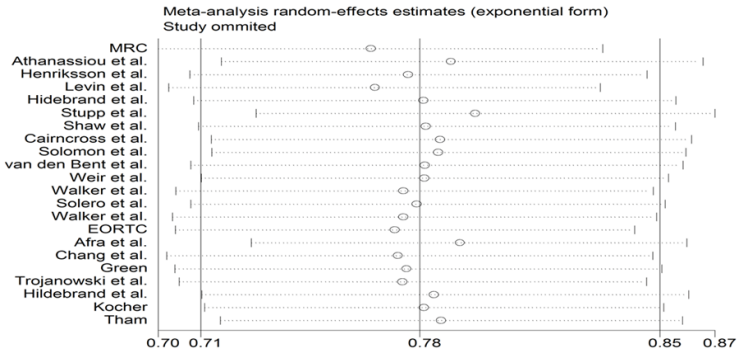

Figure 4. The plot of result of sensitivity analysis for OS.

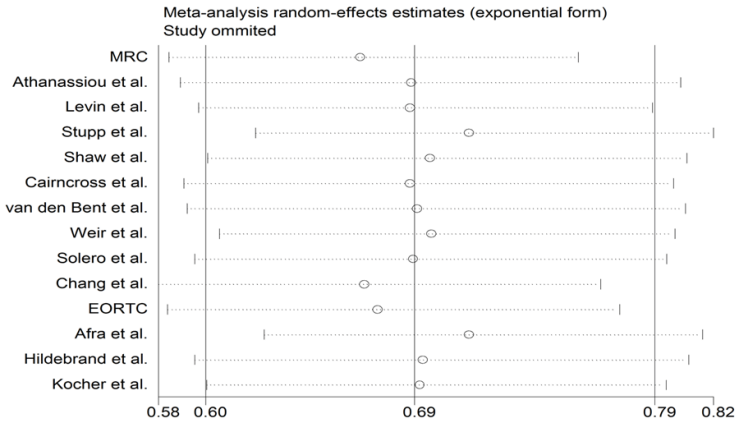

Figure 5. The plot of result of sensitivity analysis for PFS.

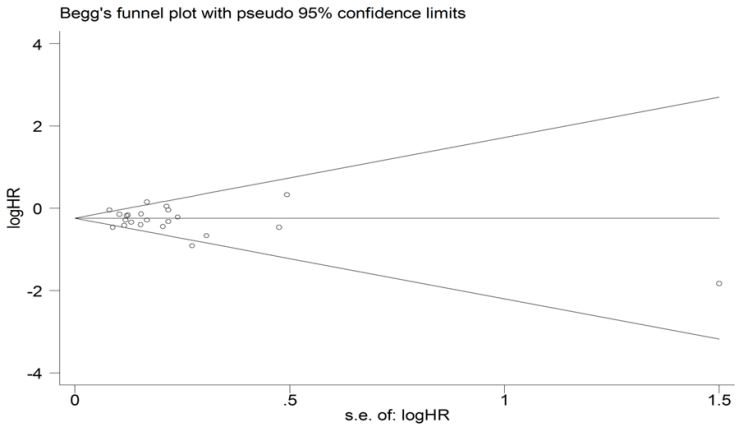

Figure 6. The Begg's funnel plot for publication bias of OS. SE standard error.

ment would not affect the efficacy of chemotherapy for treatment of malignant glioma. In particular, the chemotherapy would not prolong the OS rate for the glioma patients with biopsy (HR = 0.79, 95% CI [0.55-1.12]) or partial resection (HR = 0.91, 95% CI [0.38-2.15]). And it suggested that chemotherapy was more suitable for patients with complete resection (HR = 0.65, 95% CI [0.48-0.87]). The results of subgroup analysis also showed that TMZ (HR = 0.63, 95% CI [0.55-0.72]) or procarbazine, lomustine, and vincristine (PCV) (HR = 0.83, 95% CI [0.74-0.94]) plus RT will help prolong the OS rate compared with RT alone. However, the OS rate was not different between the BCNU/CCNU plus RT group and RT alone group (HR = 0.88, 95% CI [0.76-1.02]). The relevant results of subgroups analyses were listed in **Table 5**.

Sensitivity analysis and publication bias

The sensitivity analysis suggested that there was no significant influence observed in the results of meta-analysis of OS (**Figure 4**) and PFS (**Figure 5**). Neither publication bias nor asymmetry on visual inspection was detected for the OS (**Figure 6**) and PFS (**Figure 7**) by application of the Egger's test and the Begg's funnel plot.

Discussion

Primary malignant brain tumors occur at an annual rate of almost 4.5 cases per 100,000 population, and 43% of these cases are diagnosed as malignant gliomas [25]. The common malignant gliomas include glioblastoma multiforme, anaplastic astrocytoma, and malignant astrocytoma [29]. The prognosis of these tumors are exactly fatal, with a historical median survival of 6 months [30].

There were many randomized trials to investigate the RT plus chemotherapy versus RT alone for the treatment of malignant gliomas in recent years. However, the usefulness of adjuvant chemotherapy in the treatment of malignant gliomas remains controversial in adults. Levin

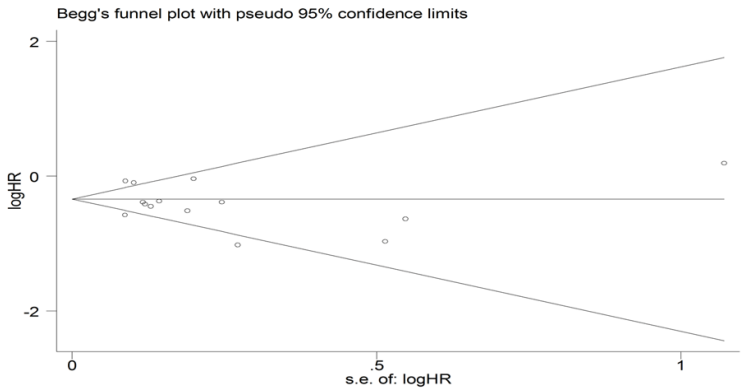

Figure 7. The Begg's funnel plot for publication bias of PFS. SE standard error.

et al. reported that marimastat did not improve survival in patients with glioblastoma or gliosarcoma following surgery and radiotherapy [12]. Shaw et al. considered that PCV plus RT improve the OS compared with RT alone [11].

Meta-analysis is a quantitative technique to evaluate clinical effects based on a series of trials on the same topic. The time-to-event analyses is particularly important for a disease such as malignant glioma, because prolongation of survival rather than cure is expected. It helps us to assess whether chemotherapy may be more or less effective in the treatment of malignant gliomas [7]. In this meta-analysis, we collected the HRs of 22 randomized trials involving 5.021 patients to detect the effectiveness of RT plus chemotherapy. Our meta-analysis showed that RT plus chemotherapy had a longer OS and PFS than RT alone in the treatment of malignant gliomas after surgery.

As the infiltrative growth of malignant gliomas, radical surgery and high dose of local irradiation usually will not improve the survival rate. As the special blood-brain barrier exists in the brain, the effectiveness of chemotherapy drugs are not originally expected. In recent decades, there were many randomized trials explore the reliability of the chemotherapy plus RT in the treatment of malignant gliomas. Before 2000, the commonly used chemotherapy drugs were BCNU and CCNU. However, the curative effect was controversial. A study from european organization for research on treatment of cancer (EORTC) brain tumor group suggested that CCNU used as adjuvant chemotherapy did not prolong the free interval [24]. Walker et al. also considered that there was no significant difference in this study between patients receiving BCNU and radiotherapy versus radiotherapy alone [25]. Recent years, some new chemotherapy drugs were developed, and the clinical trials have shown encouraging results in the treatment of patients with malignant gliomas. Solomon et al. reported that nimotuzumab showed an excellent safety profile and significant survival benefit in combination with irradiation [9]. The study from van den Bent et al. also considered that the addition of PCV after RT increased both OS and PFS in anaplastic oligodendroglial tumors [13]. Furthermore, it is worth noting that the main limiting factor of this chemotherapy is hematological toxicity. In previous studies, the nadir of leukocyte and platelet counts were often observed in patients.

The subgroup analyses indicated that the dose of radiation and age would not affect the efficacy of chemotherapy for patients with malignant glioma. A study from medical research council (MRC) brain tumor working party considered that the OS rate in 45 Gy dose of RT is higher than it in 69 Gy dose [18]. The results of subgroup analyses suggested that anaplastic glioma was sensitive for chemotherapy drugs compared with astrocytoma and GBM. Moreover, the results also considered that chemotherapy was helpless for patients with biopsy or partial resection, which may be due to incomplete resection increase recurrence rate. The gene polymorphism sties may also affect the effectiveness of chemotherapy. Some studies suggested that the codeletion of chromosomes 1p/19q was a prognostic biomarker, which predicted that the tumor grows slowly and was sensitive to chemotherapy drugs [13, 31]. According to our results, the molecular assessment would not affect the OS rate. However, Zhao et al. suggested that the codeletion of 1p/19q is associated with better survival rates in patients with gliomas [31]. There was a great difference in sensitivity to chemotherapy drugs between different patients. The subgroup analyses indicated that BCNU/CCNU plus chemotherapy would not prolong the OS rate. However, the PCV chemotherapy that included BCNU and

CCNU would improve the overall outcome. It also remind us that curative effect of combination of different drugs is better than single alone. Actually, whether other factors such as surgical resection, performance status, pathology of gliomas, and neurologic function will affect the curative effect of chemotherapy drugs or not, it should be noted in the future studies.

In conclusion, RT plus chemotherapy prolonged the OS and PFS rate compared with RT alone in the treatment of malignant gliomas. However, the results of this meta-analysis must be interpreted carefully because of heterogeneity between studies. We are looking for more double-blind trials comparing the efficacy and safety of adjuvant chemotherapy in the treatment of malignant gliomas. Moreover, we should pay more attention to explore the effect of characteristics of patients such as histology, extent of surgery, or molecular assessment on the effective of chemotherapy.

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Disclosure of conflict of interest

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