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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 $\leq 3$ and high quality if the score was $\geq 4$.

### *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

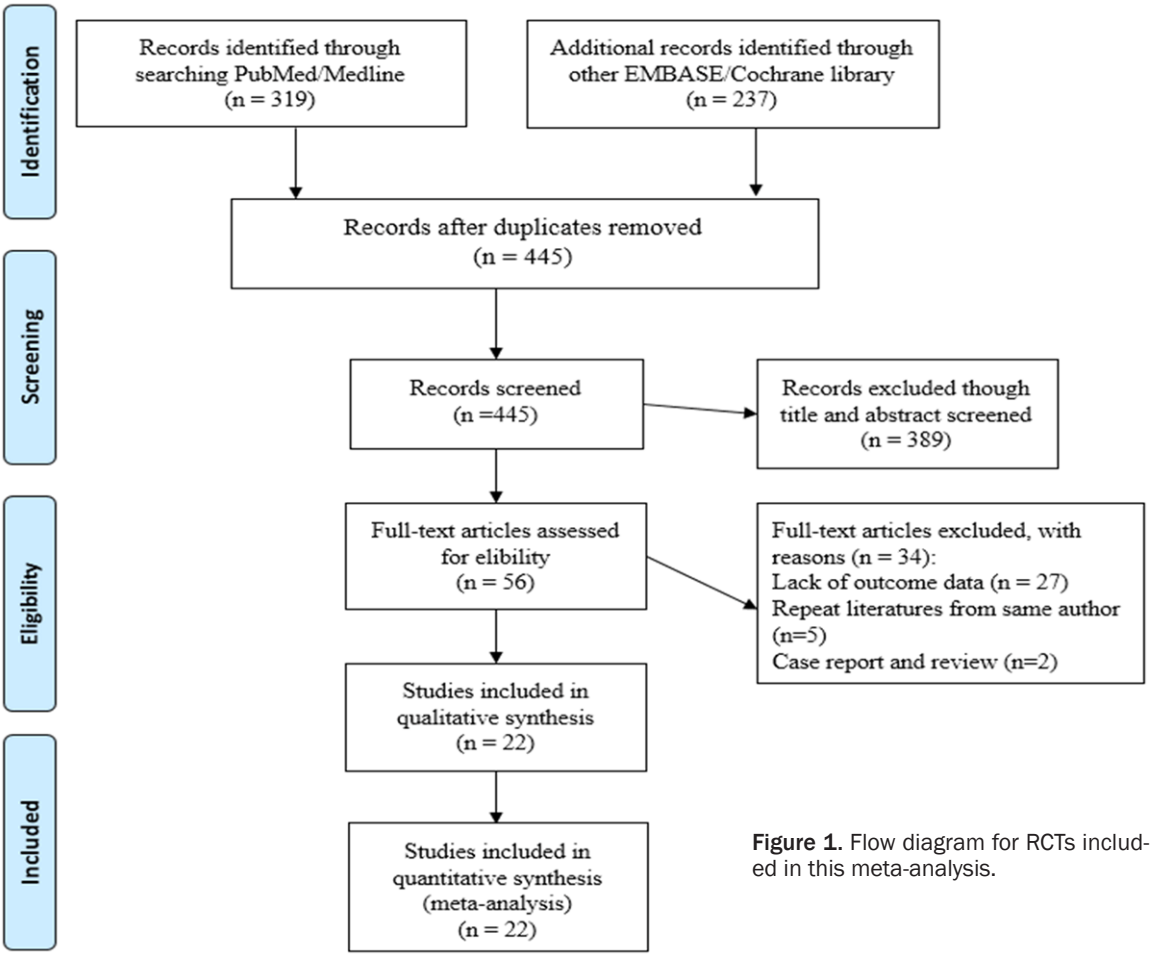


**Figure 1.** Flow diagram for RCTs included in this meta-analysis.

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.

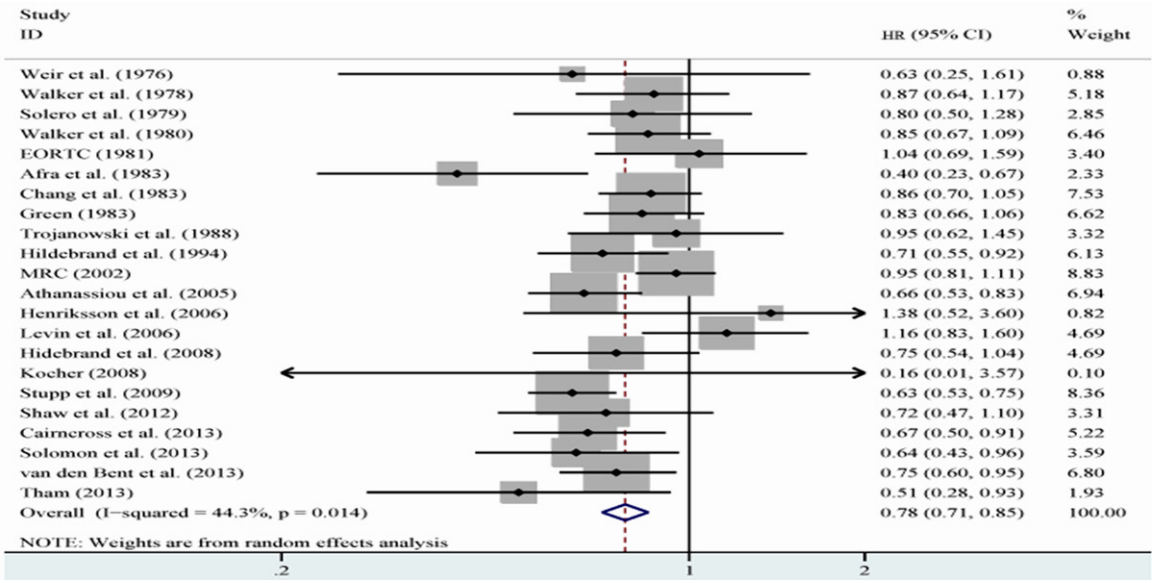


**Figure 2.** Forest plot for HRs of OS with 22 studies included in this meta-analysis.

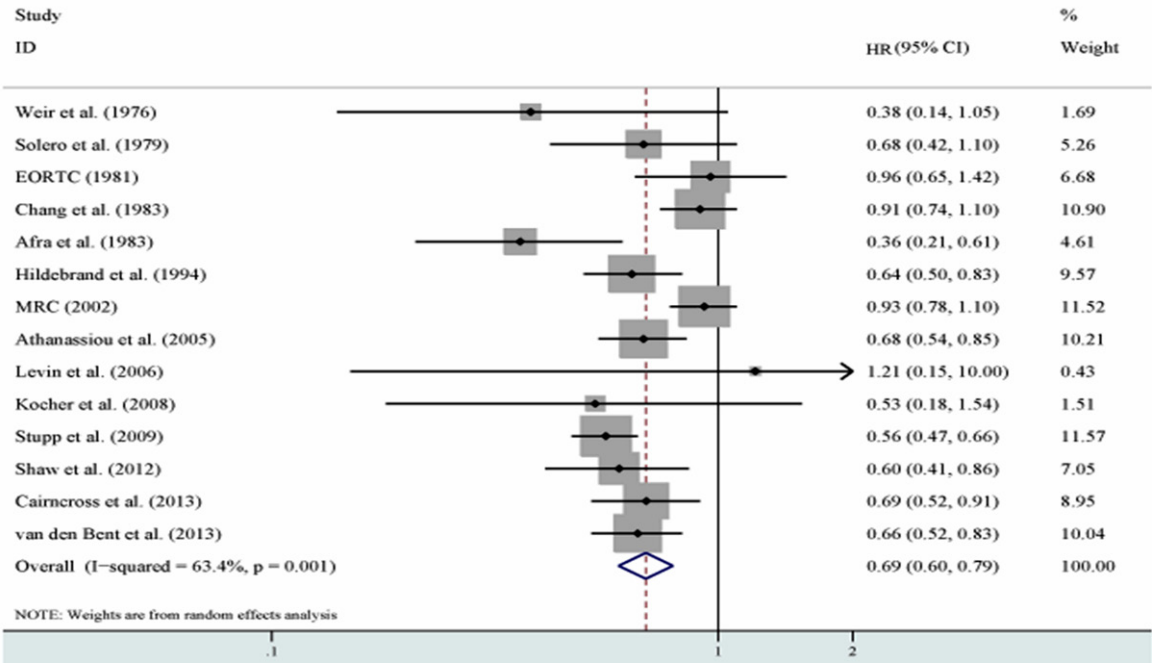


**Figure 3.** Forest plot for HRs of PFS with 14 studies included in this meta-analysis.

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-

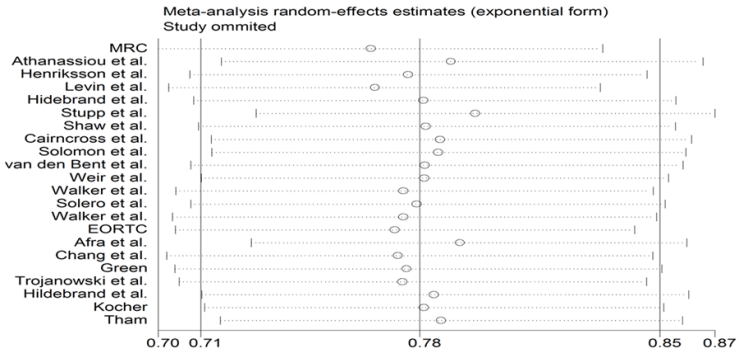


**Figure 4.** The plot of result of sensitivity analysis for OS.

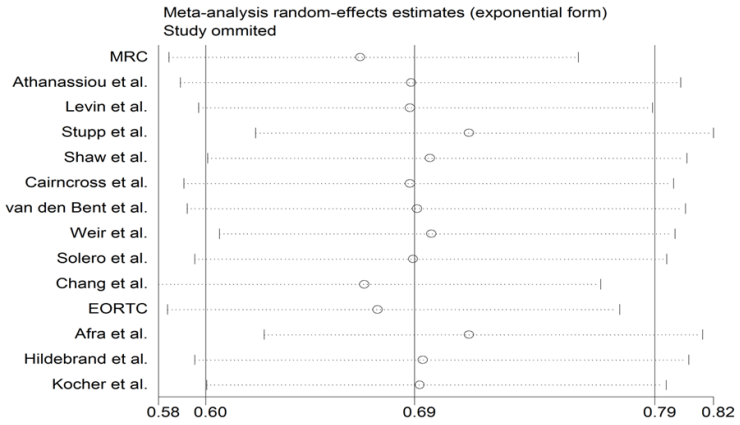


**Figure 5.** The plot of result of sensitivity analysis for PFS.

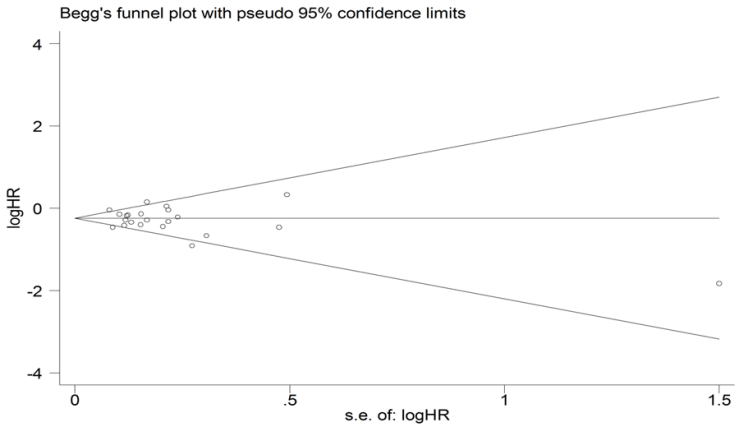


**Figure 6.** The Begg's funnel plot for publication bias of OS. SE standard error.

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

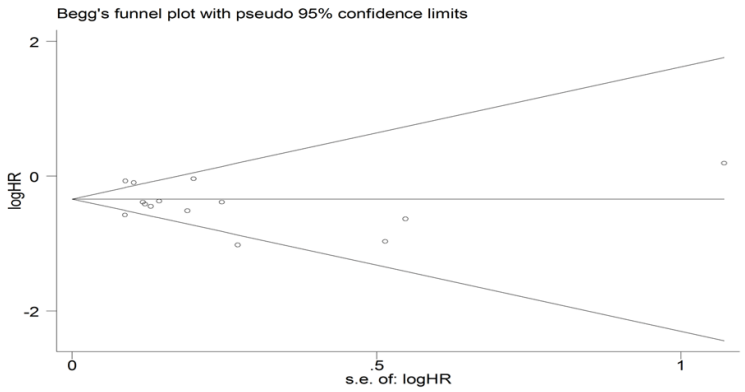


**Figure 7.** The Begg's funnel plot for publication bias of PFS. SE standard error.

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

None.

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## References

[1] Cohen AL, Colman H. Glioma biology and molecular markers. Cancer Treat Res 2015; 163: 15-30.

[2] Ashby LS, Ryken TC. Management of malignant glioma: steady progress with multimodal approaches. Neurosurg Focus 2006; 20: E3.

[3] Hutterer M, Hattingen E, Palm C, Proescholdt MA, Hau P. Current standards and new concepts in MRI and PET response assessment of antiangiogenic therapies in high-grade glioma patients. Neuro Oncol 2015; 17: 784-800.

[4] Simonetti G, Gaviani P, Innocenti A, Botturi A, Lamperti E, Silvani A. Update on treatment strategies for anaplastic glioma: a review of literature. Neurol Sci 2014; 35: 977-81.

[5] Hildebrand J, Gorlia T, Kros JM, Afra D, Frenay M, Omuro A, Stupp R, Lacombe D, Allgeier A, van den Bent MJ. Adjuvant dibromodulcitol and BCNU chemotherapy in anaplastic astrocytoma: Results of a randomised European Organisation for Research and Treatment of Cancer phase III study (EORTC study 26882). Eur J Cancer 2008; 44: 1210-6.

[6] Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10: 459-66.

[7] Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet 2002; 359: 1011-8.

[8] Zhang L, Wu X, Xu T, Luo C, Qian J, Lu Y. Chemotherapy plus radiotherapy versus radiotherapy alone in patients with anaplastic glioma: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2013; 139: 719-26.

[9] Solomon MT, Selva JC, Figueredo J, Vaquer J, Toledo C, Quintanal N, Salva S, Domingez R, Alert J, Marinello JJ, Catala M, Griego MG, Martell JA, Luaces PL, Ballesteros J, de-Castro N, Bach F, Crombet T. Radiotherapy plus nimotuzumab or placebo in the treatment of high grade glioma patients: results from a randomized, double blind trial. BMC Cancer 2013; 13: 299.

[10] Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, Fink K, Souhami L, Laperriere N, Curran W, Mehta M. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: Long-term results of RTOG 9402. J Clin Oncol 2013; 31: 337-43.

[11] Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, Barger GR, Brown PD, Gilbert MR, Mehta MP. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: Initial results of RTOG 9802. J Clin Oncol 2012; 30: 3065-70.

[12] Levin VA, Phuphanich S, Yung WK, Forsyth PA, Maestro RD, Perry JR, Fuller GN, Baillet M. Randomized, double-blind, placebo-controlled trial of marimastat in glioblastoma multiforme patients following surgery and irradiation. J Neurooncol 2006; 78: 295-302.

[13] van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY,

Bernsen HJ, Frenay M, Tijssen CC, Grisold W, Sipos L, Enting RH, French PJ, Dinjens WN, Vecht CJ, Allgeier A, Lacombe D, Gorlia T, Hoang-Xuan K. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013; 31: 344-50.

[14] Tham CK, See SJ, Tan SH, Lim KH, Ng WH, Thomas J, Chong DQ, Chua ET. Combined temozolomide and radiation as an initial treatment for anaplastic glioma. Asia Pac J Clin Oncol 2013; 9: 220-5.

[15] Kocher M, Frommolt P, Borberg SK, Ruhl U, Steingraber M, Niewald M, Staar S, Stuschke M, Becker G, Fischedick AR, Herfarth K, Grauthoff H, Muller RP. Randomized study of postoperative radiotherapy and simultaneous temozolomide without adjuvant chemotherapy for glioblastoma. Strahlenther Onkol 2008; 184: 572-9.

[16] Henriksson R, Malmstrom A, Bergstrom P, Bergh G, Trojanowski T, Andreasson L, Blomquist E, Jonsborg S, Edekling T, Salander P, Brannstrom T, Bergenheim AT. High-grade astrocytoma treated concomitantly with estramustine and radiotherapy. J Neurooncol 2006; 78: 321-6.

[17] Athanassiou H, Synodinou M, Maragoudakis E, Paraskevaidis M, Verigos C, Misailidou D, Antonadou D, Saris G, Beroukas K, Karageorgis P. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. J Clin Oncol 2005; 23: 2372-7.

[18] Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. J Clin Oncol 2001; 19: 509-18.

[19] Hildebrand J, Sahmoud T, Mignolet F, Brucher JM, Afra D. Adjuvant therapy with dibromodulcitol and BCNU increases survival of adults with malignant gliomas. EORTC Brain Tumor Group. Neurology 1994; 44: 1479-83.

[20] Trojanowski T, Peszynski J, Turowski K, Kaminski S, Goscinski I, Reinfus M, Krzyszkowski T, Pyrich M, Bielawski A, Leszczyk C. Postoperative radiotherapy and radiotherapy combined with CCNU chemotherapy for treatment of brain gliomas. J Neurooncol 1988; 6: 285-91.

[21] Green SB, Byar DP, Walker MD, Pistenmaa DA, Alexander E Jr, Batzdorf U, Brooks WH, Hunt WE, Mealey J Jr, Odom GL, Paoletti P, Ransohoff J 2nd, Robertson JT, Selker RG, Shapiro WR, Smith KR Jr, Wilson CB, Strike TA. Comparisons of carmustine, procarbazine, and high-dose methylprednisolone as additions to surgery and radiotherapy for the treatment of malignant glioma. Cancer Treat Rep 1983; 67: 121-32.

[22] Chang CH, Horton J, Schoenfeld D, Salazer O, Perez-Tamayo R, Kramer S, Weinstein A, Nelson JS, Tsukada Y. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. Cancer 1983; 52: 997-1007.

[23] Afra D, Kocsis B, Dobay J, Eckhardt S. Combined radiotherapy and chemotherapy with dibromodulcitol and CCNU in the postoperative treatment of malignant gliomas. J Neurosurg 1983; 59: 106-10.

[24] Evaluation of CCNU, VM-26 plus CCNU, and procarbazine in supratentorial brain gliomas. Final evaluation of a randomized study. European Organization for Research on Treatment of Cancer (EORTC) Brain Tumor Group. J Neurosurg 1981; 55: 27-31.

[25] Walker MD, Green SB, Byar DP, Alexander E Jr, Batzdorf U, Brooks WH, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, Owens G, Ransohoff J 2nd, Robertson JT, Shapiro WR, Smith KR Jr, Wilson CB, Strike TA. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 1980; 303: 1323-9.

[26] Solero CL, Monfardini S, Brambilla C, Vaghi A, Valagussa P, Morello G, Bonadonna G. Controlled study with BCNU vs. CCNU as adjuvant chemotherapy following surgery plus radiotherapy for glioblastoma multiforme. Cancer Clin Trials 1979; 2: 43-8.

[27] Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, Norrell HA, Owens G, Ransohoff J, Wilson CB, Gehan EA, Strike TA. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg 1978; 49: 333-43.

[28] Weir B, Band P, Urtasun R, Blain G, McLean D, Wilson F, Mielke B, Grace M. Radiotherapy and CCNU in the treatment of high-grade supratentorial astrocytomas. J Neurosurg 1976; 45: 129-34.

[29] Yin AA, Cai S, Dong Y, Zhang LH, Liu BL, Cheng JX, Zhang X. A meta-analysis of temozolomide versus radiotherapy in elderly glioblastoma patients. J Neurooncol 2014; 116: 315-24.

[30] Oh T, Sayegh ET, Fakurnejad S, Oyon D, Lamano JB, DiDomenico JD, Bloch O, Parsa AT. Vaccine therapies in malignant glioma. Curr Neurol Neurosci Rep 2015; 15: 508.

[31] Zhao J, Ma W, Zhao H. Loss of heterozygosity 1p/19q and survival in glioma: a meta-analysis. Neuro Oncol 2014; 16: 103-12.