Temozolomide Combined with Radiotherapy Can Benefit Patients with Glioma: A Systematic Review and Meta-Analysis

Qinhong huang  
The National Key Clinical Specialty; Guangdong Provincial Key Laboratory On Brain Function Repair and Regeneration, Department of Neurosurgery, Zhujiang Hospital, Southern Medical University

Lihui Yang  
Guangzhou Medical University

Zhenwei Ye  
Guangzhou Medical University

Jing Yang  
The First Affiliated Hospital of Shantou University, Shantou University, Shantou, 515041, China

Yiquan Ke (kyquan@smu.edu.cn)  
The National Key Clinical Specialty; Guangdong Provincial Key Laboratory On Brain Function Repair and Regeneration, Department of Neurosurgery, Zhujiang Hospital, Southern Medical University

Research Article

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Abstract

Background: Glioma originates from glial cells of the nervous system and is the most common malignant tumor in the brain. Temozolomide is considered as a promising medicine that can improve the overall survival (OS) and progress-free survival (PFS) rate of patients with glioma after operation. However, whether radiotherapy plus temozolomide has substantive role for glioma patients remains controversial.

Methods: We conducted a meta-analysis included 10 Randomized controlled trials (RCTs) encompassing 2703 patients to evaluate the efficacy and safety of radiotherapy plus temozolomide for glioma. EMbase, PubMed, Web of Science, and Cochrane library were searched. Our study strictly follows the PRISMA guideline.

Results: Overall, compared with receiving radiotherapy alone, patients through radiotherapy combined with temozolomide has substantial benefit on both OS (HR=0.78; 95% CI: 0.62-0.98; P =0.03) and PFS (HR=0.62; 95% CI: 0.49-0.78; P <0.0001). The best effect shows in patients receiving radiotherapy combined with both concurrent and adjuvant temozolomide on both OS (HR=0.66; 95% CI: 0.58-0.74; P <0.00001) and PFS (HR=0.55; 95% CI: 0.48-0.62; P <0.00001), when compared with radiotherapy alone. Whereas, temozolomide monotherapy do not show greater benefits than radiotherapy alone on OS (HR=0.93; 95% CI: 0.74-1.14; P =0.53). Moreover, radiotherapy plus temozolomide obviously increase the incidence of hematological complications than only radiotherapy (RR=10.31; 95% CI: 4.49-23.71; P<0.00001). Also, our meta-analysis suggested that MGMT methylation test can be helpful for evaluating prognosis, determining individualized treatment and forecasting the curative effect.

Conclusion: Radiotherapy combined with temozolomide, especially combined with both concurrent and adjuvant temozolomide has great benefit on both OS and PFS of glioma patients. Conditionally, patients with glioma receiving glioma MGMT methylation test have advantage over evaluating prognosis, determining individualized treatment and forecasting the curative effect. Last but not least, monitoring blood routine andremedying the possible abnormalities in time is especially necessary of patient receiving temozolomide therapy.

Introduction

Glioma originating from glial cells, is the most common primary tumor in the brain, and accounts for 81% of malignant tumor in central nervous system (Ostrom et al., 2018, Zhang et al., 2012b). Patients with glioma have poor prognosis; even in low-grade glioma patients, the 10-year survival rate is just 47% with a median survival time of 11.6 years, let alone patients with high-grade glioma (Ohgaki and Kleihues, 2005). Unfortunately, there is no ideal therapy strategy that can help patients reach a complete remission (Xu et al., 2020).

Current therapy strategy on glioma including operation resection, temozolomide and radiotherapy, whereas they are still far from reach an ideal curative effect (Nabors et al., 2017). Temozolomide, a kind of chemotherapy medicine, is considered as a promising drug for glioma. Lots of clinical trials have
reported its significant effect on the OS and PFS of patients with glioma (Karacetin et al., 2011, Malmström et al., 2017, Perry et al., 2017, Stupp et al., 2009). However, there are still lacking of robust evidence to support routine clinical use of temozolomide combined with radiotherapy for glioma, and the combination pattern of temozolomide and radiotherapy remains controversial in academia. Recent original studies have explored the efficacy and safety of radiotherapy plus temozolomide for treating glioma patients, but the results are conflicting (Hwang et al., 2020, Malmström et al., 2017, Perry et al., 2017, Tesileanu et al., 2022). Our meta-analysis included 10 RCTs, aiming to ensure the efficacy and safety of radiotherapy plus temozolomide for treating glioma patients.

Methods

This meta-analysis followed a prespecified protocol which was registered on PROSPERO (PROSPERO 2022: CRD42022373068).

Literature search

We performed a systematical literature search before October 23, 2022 in EMbase, PubMed, Web of Science, and Cochrane library, following the PRISMA guideline. The search terms included “glioma”, “radiotherapy” and “temozolomide without any restrictions for data and language. Also, reference lists of relevant articles are reviewed.

Inclusion and exclusion criteria

2726 records were identified. After duplicates removed, 1956 articles were selected, screened from title and abstract, and then 129 full-text related articles were assessed for eligibility. Finally, 10 articles were included in our analysis.

The inclusion criteria are as follows: (1) the studies are RCTs; (2) Patients with newly diagnosed or histologically confirmed glioma; (3) intervention treatments only contain temozolomide and radiotherapy; (4) intervention treatments are temozolomide combined with/not with radiotherapy versus only radiotherapy.

The exclusion criteria are as follows: (1) studies are not RCTs; (2) studies do not provide the both hazard ratios (HRs) for Overall survival (OS) and Progression-free survival (PFS); (3) the post type of the study was system review, case report, letter to editor or expert opinion.

Data extraction and quality assessment
Two independent reviewers (Lihui Yang and Zhenwei Ye) selected the articles and checked whether they meet the inclusion and exclusion criteria. Some important information of the inclusive studies was extracted: (1) some general information such as first author and publication year; (2) some baseline information such as number of patients, age and sex; (3) indispensable information for our analysis including detail intervention treatments in each study, HRs for OS and PFS in different intervention treatments, MGMT promoter status of the patients and adverse effects. Risk of bias was assessed by using Cochrane Risk of Bias Tool. Any disagreements were solved through discussion and finally reach a consensus.

Type of outcomes

Primary outcome: HRs for OS and PFS in different intervention treatments.

Secondary outcome: (1) the impact of O6-methylguanine-DNA methyltransferase (MGMT) promoter status on HRs for OS and PFS; (2) relative risk (RR) of adverse effects in in different intervention treatments.

**Statistical analysis**

We assess HRs for OS and PFS, and RRs for adverse effects and hematological complications. Both HR and RR were assessed with 95% confidence interval (CI) for dichotomous outcomes. We also assess HR for OS in patients with MGMT methylated glioma and with MGMT unmethylated glioma respectively. Our analysis does not assess publication bias, because the included studies is not more than 10. All the analysis results were presented as forest plots, with heterogeneity assessed using the I-squared statistic. If heterogeneity (I-squared value >50%), random-effects model was used; Otherwise, fixed-effects model was chosen. All the statistical analyses were performed in RevMan 5.4 software. All P values less than 0.05 are considered statistically significantly.

**Results**

**Search results, study characteristics and risk of bias assessment**

2726 records were identified. After removing the duplicated results and screening the titles and abstracts of all studies, 129 full-text articles were selected for the next stage of evaluation. Finally, under the guidance of strict inclusion or exclusion criteria, we selected 10 RCTs for our analysis (Baumert et al., 2016, Hegi et al., 2005, Hwang et al., 2020, Karacetin et al., 2011, Malmström et al., 2012, Malmström et
The characteristics of 10 selected RCTs were presented in Table 1. The total sample size is 2703 without duplication, and 2 of the studies involve the same group of participants but focus on different point (Hegi et al., 2005, Stupp et al., 2009). A study (Malmström 2012) was selected three times in our analysis because three comparisons with research value are involved (Malmström et al., 2012). The control groups of all the studies are patients receiving radiotherapy alone. There are 3 studies using temozolomide monotherapy (Baumert et al., 2016, Malmström et al., 2012, Wick et al., 2012) as research groups. There are 6 studies using temozolomide combined with radiotherapy as research groups (Hwang et al., 2020, Karacetin et al., 2011, Malmström et al., 2017, Perry et al., 2017, Stupp et al., 2009, Tesileanu et al., 2022), and 4 of them use radiotherapy with both concurrent and adjuvant temozolomide as treatment (Hwang et al., 2020, Karacetin et al., 2011, Perry et al., 2017, Stupp et al., 2009).

The risk of bias was assessed including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting. All trials were randomized, but all the trials do not provide any information on allocation concealment, blinding and incomplete outcome data. The risk of bias was moderate and all 10 studies have high-quality based on the quality assessment. More details are presented in Fig 2.

**Effect of temozolomide monotherapy**

In this part of analysis, 3 trials were selected, 1 of them were included twice because it contains the comparison between treatments with temozolomide alone and different dosage of radiotherapy. Our result shows that compared with receiving radiotherapy alone, patients with glioma receiving temozolomide alone for therapy has no significantly impact on OS (HR=0.93; 95% CI: 0.74-1.14; P =0.53) (Fig.3)

**Effect of radiotherapy combined with temozolomide**

In this part of analysis, we included the trials whose research group receiving radiotherapy combined with temozolomide, no matter concurrent, adjuvant or both concurrent and adjuvant temozolomide. Our result shows that compared with receiving radiotherapy alone, patients with glioma through radiotherapy combined with temozolomide has substantial benefit on both OS (HR=0.78; 95% CI: 0.62-0.98; P =0.03) and PFS (HR=0.62; 95% CI: 0.49-0.78; P <0.0001) (Fig. 4).

For further analyze the effect of radiotherapy combined with temozolomide, in this stage, we only included the researched group receiving radiotherapy combined with both concurrent and adjuvant temozolomide. Much greater benefit is found on both OS (HR=0.66; 95% CI: 0.58-0.74; P <0.00001) and PFS (HR=0.55; 95% CI: 0.48-0.62; P <0.00001) (Fig. 5).

**The influence of MGMT promoter status on curative effect**
Because MGMT plays important role in DNA repair and has interaction with temozolomide-alkylated DNA, we analyze the influence of MGMT promoter status on curative effect.

Firstly, we conduct an analysis on the HR for OS of patients with MGMT methylated glioma versus MGMT unmethylated glioma regardless what kind of treatments are used. Our result shows that there is substantial impact on the OS (HR=0.56; 95% CI: 0.46-0.69; P <0.00001) (Fig. 6A). Then, we conduct an analysis on the HR for OS of patients with MGMT methylated glioma receiving treatment containing temozolomide versus radiotherapy alone. Also, great benefit is presented on OS (HR=0.67; 95% CI: 0.45-0.98; P =0.04) (Fig. 6B). Last, we analyze the HR for OS of patients with MGMT unmethylated glioma receiving treatment containing temozolomide versus radiotherapy alone. However, only marginally benefit presents on OS (HR=0.83; 95% CI: 0.69-1.00; P =0.05) (Fig. 6C). Because of the heterogeneity of the included studies in this part is low ($I^2=28$), the final result should not be greatly different in random-effects model and fixed-effects model, so we use the random-effects model to analyze again. As expected, the result of HR for OS is almost the same as that in fixed-effects model, but the borderline significance of the improved OS disappeared (HR=0.84; 95% CI: 0.67-1.05; P =0.12) (Fig. 6D).

Hematological toxicity and non-hematological toxic

In order to ensure the safety of temozolomide for therapy, in this part, we conducted an analysis on the hematological toxicity and non-hematological toxic. Compared with radiotherapy alone, patients with glioma receiving therapy that contains temozolomide have higher risk of developing hematological complications (RR=10.31; 95% CI: 4.49-23.71; P<0.00001) (Fig.7A). However, only subtle increase the risk of developing non-hematological complications is observed when comparing therapy containing temozolomide with radiotherapy alone (RR=10.31; 95% CI: 4.49-23.71; P<0.00001) (Fig.7B).

Discussions

Although it still remains controversial, using radiotherapy plus temozolomide for postoperative therapy has been established as the standard of care for malignant glioma, known colloquially as the Stupp protocol (Stupp et al., 2007). As a kind of prodrug alkylating agent, temozolomide can easily rosses the blood-brain barrier, leading to cytotoxic effect on tumor cells by adding methyl groups to purines and pyrimidines in DNA (Zhang et al., 2012a).

Our analysis suggests that radiotherapy plus temozolomide, no matter how to combined them, can significantly improve the HR for OS (HR=0.78; 95% CI: 0.62-0.98; P=0.03) and PFS (HR=0.62; 95% CI: 0.49-0.78; P<0.0001) as compared to radiotherapy alone. Among all kinds of combinations, radiotherapy combined with both concurrent and adjuvant temozolomide is the most common, and this kind of combination presents obviously greater benefit on OS (HR=0.66; 95% CI: 0.58-0.74; P<0.00001) and PFS
(HR=0.55; 95% CI: 0.48-0.62; P<0.00001) as compared to radiotherapy alone. But it is noteworthy that, our analysis also shows that when compared with radiotherapy alone, temozolomide monotherapy cannot show better effect on OS (HR=0.93; 95% CI: 0.74-1.14; P=0.53). Based on the results above, we suggested that in order to reach the best curative effect, combining radiotherapy with concurrent and adjuvant temozolomide as postoperative therapy is a promising strategy, while there is no substantial difference between temozolomide monotherapy and radiotherapy alone, though both of them have certain benefits for glioma patients.

The curative effect of temozolomide can be affected by the gene expression of tumor cells. Among them, MGMT is the most influential one whose encoded protein can repair temozolomide-alkylated DNA by removing methyl groups from DNA at the O6 position (Gerson, 2004). It has reported that nearly 55% of glioblastoma patients are resistant to temozolomide because of their MGMT DNA repair system (Hegi et al., 2005). MGMT transcription can be inhibits when its promoter is methylated, therefore, patients with MGMT methylated glioma may benefits from temozolomide more(Esteller et al., 1999, Mansouri et al., 2019). Overall, our analysis shows that regardless what kind of treatments are used, patients with MGMT methylated have substantial impact on OS (HR=0.56; 95% CI: 0.46-0.69; P<0.00001) than MGMT unmethylated glioma. Moreover, patients with MGMT methylated glioma benefits greater from therapy containing temozolomide (including temozolomide monotherapy) than radiotherapy alone, according to significantly higher OS (HR=0.67; 95% CI: 0.45-0.98; P=0.04); whereas in patients with MGMT unmethylated glioma, therapy containing temozolomide shows no substantive benefit on OS (HR=0.84; 95% CI: 0.67-1.05; P=0.12) when compared with radiotherapy alone. The results above shows that patients with MGMT methylated glioma have a longer OS and achieve better curative effect from temozolomide, reflecting the better prognosis. So, we proposed that conditionally conducting MGMT methylation test for glioma patients is a good choice to evaluate prognosis, determine individualized treatment and forecast the curative effect.

As a kind of chemotherapy medicine, the use of temozolomide must be safety enough. Our study also conducts an analysis on the safety of temozolomide, whose results indicated that patients receiving therapy containing temozolomide suffer from significantly higher risk of developing hematological complications than those receiving radiotherapy alone (RR=10.31; 95% CI: 4.49-23.71; P<0.00001). Fortunately, there is no difference in non-hematological adverse events between patients receiving therapies that contain temozolomide or not. Therefore, we proposed that it is essential to monitor blood routine and remedy the possible abnormalities in time for glioma patients receiving temozolomide as therapy.

**Conclusion**
Radiotherapy combined with temozolomide, especially combined with both concurrent and adjuvant temozolomide has great benefit on both OS and PFS of glioma patients. Conditionally, patients with glioma receiving glioma MGMT methylation test have advantage over evaluating prognosis, determining individualized treatment and forecasting the curative effect. Last but not least, monitoring blood routine and remedying the possible abnormalities in time is especially necessary of patient receiving temozolomide therapy.

**Declarations**

**Authors' contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

**Acknowledgements**

None.

**Conflict of Interest Statement**

The author reports no conflicts of interest in this work.

**Funding:**

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**Availability of data and materials**

All articles were retrieved in Pubmed, Embase and Cochrane. All the data that we used can be found in the original studies that included in our meta-analysis.

**Ethics approval and consent to participate**
Consent for publication

All authors have read and approved the manuscript.

References


**Table**

Table 1 is available in the Supplementary Files section.

**Figures**
Flowcharts of study search and selection

Figure 1

Flowcharts of study selection and search.
Figure 2

Risk of bias summary: The judgments of 2 independent reviewers about each risk of bias item for each included study (A). Risk of bias graph: The judgments of 2 independent reviewers judgments about each risk of bias item presented as percentages across all included studies (B).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
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<tr>
<td>Baumert 2016</td>
<td>0.1484</td>
<td>0.1295</td>
<td>26.0%</td>
<td>1.16 [0.90, 1.50]</td>
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<td>Malmström 2012 (1)</td>
<td>-0.3567</td>
<td>0.1517</td>
<td>23.2%</td>
<td>0.70 [0.52, 0.94]</td>
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<td>Malmström 2012 (2)</td>
<td>-0.1985</td>
<td>0.1345</td>
<td>25.3%</td>
<td>0.82 [0.63, 1.07]</td>
</tr>
<tr>
<td>Wick 2012</td>
<td>0.3862</td>
<td>0.1329</td>
<td>25.5%</td>
<td>1.09 [0.84, 1.41]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.93 [0.74, 1.17]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 8.69, df = 3$ ($P = 0.03$); $I^2 = 65\%$
Test for overall effect: $Z = 0.62$ ($P = 0.53$)

Figure 3

Forest plot for the meta-analysis of OS: temozolomide monotherapy vs. radiotherapy alone.
Figure 4

Forest plot for the meta-analysis of OS (A) and PFS (B): radiotherapy combined with temozolomide vs. radiotherapy alone.
Figure 5

Forest plot for the meta-analysis of OS (A) and PFS (B): radiotherapy combined with concurrent and adjuvant temozolomide vs. radiotherapy alone.

**A**

<table>
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<th>Study or Subgroup</th>
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<td>Hwang 2020</td>
<td>-0.9163</td>
<td>0.4074</td>
<td>1.1%</td>
<td>0.40 [0.18, 0.89]</td>
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<tr>
<td>Marmström 2017</td>
<td>-0.6039</td>
<td>0.2322</td>
<td>18.7%</td>
<td>0.52 [0.33, 0.82]</td>
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<tr>
<td>Stupp 2009</td>
<td>-0.7133</td>
<td>0.2174</td>
<td>21.3%</td>
<td>0.49 [0.32, 0.75]</td>
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<td>Tesileanu 2022</td>
<td>-0.4308</td>
<td>0.1876</td>
<td>28.6%</td>
<td>0.65 [0.45, 0.94]</td>
<td></td>
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<tr>
<td>Wick 2012</td>
<td>-0.4784</td>
<td>0.1687</td>
<td>25.5%</td>
<td>0.62 [0.42, 0.92]</td>
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Total (95% CI): 100.0% 0.56 [0.46, 0.69]

Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 4 (P = 0.73); I² = 0%

Test for overall effect: Z = 5.73 (P < 0.00001)

**B**

<table>
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<th>Study or Subgroup</th>
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<tr>
<td>Hegi 2005</td>
<td>-0.6733</td>
<td>0.2541</td>
<td>24.1%</td>
<td>0.51 [0.31, 0.84]</td>
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<td>Malmström 2012</td>
<td>-0.4463</td>
<td>0.2527</td>
<td>24.2%</td>
<td>0.64 [0.39, 1.05]</td>
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<tr>
<td>Perry 2017</td>
<td>-0.6349</td>
<td>0.1698</td>
<td>31.0%</td>
<td>0.53 [0.38, 0.74]</td>
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<tr>
<td>Tesileanu 2022</td>
<td>0.3075</td>
<td>0.3637</td>
<td>20.5%</td>
<td>1.36 [0.75, 2.47]</td>
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Total (95% CI): 100.0% 0.67 [0.45, 0.98]

Heterogeneity: Tau² = 0.10; Chi² = 8.15, df = 3 (P = 0.04); I² = 63%

Test for overall effect: Z = 2.05 (P = 0.04)

**C**

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<td>Hegi 2005</td>
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<td>22.5%</td>
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<td>Malmström 2012</td>
<td>0.1484</td>
<td>0.2013</td>
<td>22.2%</td>
<td>1.16 [0.78, 1.72]</td>
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<td>Perry 2017</td>
<td>-0.2877</td>
<td>0.1491</td>
<td>40.3%</td>
<td>0.75 [0.56, 1.00]</td>
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<td>Tesileanu 2022</td>
<td>-0.1278</td>
<td>0.2441</td>
<td>15.0%</td>
<td>0.88 [0.59, 1.42]</td>
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Total (95% CI): 100.0% 0.83 [0.66, 1.00]

Heterogeneity: Chi² = 4.15, df = 3 (P = 0.25); I² = 28%

Test for overall effect: Z = 1.96 (P = 0.05)

**D**

<table>
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<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
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<td>23.3%</td>
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<td>Malmström 2012</td>
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<td>0.2013</td>
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<td>Perry 2017</td>
<td>-0.2877</td>
<td>0.1491</td>
<td>35.2%</td>
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<td>0.2441</td>
<td>17.4%</td>
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Total (95% CI): 100.0% 0.84 [0.67, 1.05]

Heterogeneity: Tau² = 0.01; Chi² = 4.15, df = 3 (P = 0.25); I² = 28%

Test for overall effect: Z = 1.56 (P = 0.12)

Figure 6

Forest plot for the meta-analysis of OS: patients with MGMT methylated glioma vs. patients with MGMT unmethylated glioma (A); patients with MGMT methylated glioma receiving treatment contain temozolomide vs. radiotherapy alone (B); patients with MGMT unmethylated glioma receiving treatment containing temozolomide vs. radiotherapy alone (C. fixed-effects model); patients with MGMT
unmethylated glioma receiving treatment containing temozolomide vs. radiotherapy alone (D. random-effects model).

**Figure 7**

Forest plot for the meta-analysis of hematological complications (A) and non-hematological complications (B): therapy containing temozolomide vs. radiotherapy alone.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- **Table1.tif**