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Updated systematic review and meta-analysis of extended adjuvant temozolomide in patients with newly diagnosed glioblastoma

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Abstract

Background. Contemporary standard-of-care for newly diagnosed glioblastoma (GBM) is maximal safe resection followed by postoperative focal conformal radiotherapy (RT) plus concurrent temozolomide (TMZ) and 6-cycles of adjuvant TMZ (Stupp regimen). However, many patients continue to receive extended adjuvant TMZ (beyond 6-cycles) without solid scientific evidence. This review pools data from nonrandomized studies and randomized controlled trials (RCTs) comparing extended adjuvant TMZ (>6-cycles) to standard adjuvant TMZ (6-cycles) in patients with newly diagnosed GBM for updated evidence-synthesis.

Methods. This systematic review and meta-analysis was carried out in accordance with the Cochrane methodology including quality assessment of primary studies. Primary outcome of interest was comparative efficacy defined as progression-free survival (PFS) and overall survival (OS). Hazard ratios (HRs) for PFS and OS with corresponding 95% confidence interval (CIs) were extracted/computed from individual primary studies and pooled using random-effects model. Any p-value <0.05 was considered statistically significant.

Results. Evidence-synthesis was based on pooling of data from 2578 patients enrolled in 16 nonrandomized comparative studies and 5 RCTs. Overall, extended adjuvant TMZ was associated with statistically significant reduction in the risk of progression (HR = 0.72, 95%CI: 0.60–0.87; $p = 0.007$) and death (HR = 0.71, 95%CI: 0.57–0.90; $p = 0.004$) compared to standard adjuvant TMZ. However, on subgroup analysis, survival benefit of extended adjuvant TMZ was limited to data synthesized from retrospective nonrandomized comparative studies with no statistically significant difference in outcomes seen after pooling of data from RCTs only.

Conclusion. Apparent survival benefit of extended adjuvant TMZ in newly diagnosed GBM is largely driven by nonrandomized comparative studies with high inherent potential for multiple biases.

Key Points

- The optimal duration of adjuvant TMZ in newly diagnosed GBM remains uncertain.
- There is widespread variability in the number of adjuvant TMZ cycles in clinical practice.
- Updated meta-analysis pooling data from prospective and retrospective studies suggests survival benefit of extended adjuvant regimens.
- However, benefit is largely driven by nonrandomized comparative studies with inherent potential for bias and not seen in RCTs.

Importance of the Study

Contemporary standard-of-care for newly-diagnosed glioblastoma (GBM) is maximal safe resection followed by postoperative focal conformal radiotherapy (RT) plus concurrent temozolomide (TMZ) and 6-cycles of adjuvant TMZ (Stupp regimen). However, many patients continue to receive extended adjuvant TMZ (beyond 6-cycles) based on personal, physician, and institutional biases without solid scientific evidence. This systematic review and meta-analysis pools data from 2578 patients enrolled in 16 nonrandomized comparative studies and 5 randomized controlled trials (RCTs) comparing standard adjuvant TMZ (6-cycles) versus extended adjuvant TMZ (>6-cycles) in newly diagnosed GBM. Overall, extended adjuvant TMZ was associated with statistically significant reduction in the risk of progression and death compared to standard adjuvant TMZ. However, this apparent survival benefit of extended adjuvant TMZ is limited to data synthesized from retrospective non-randomized comparative studies (with inherent potential for bias) but no statistically significant difference in outcomes seen after pooling of data from RCTs only.

Gliomas are the most common malignant primary tumors of the brain with glioblastoma (GBM) comprising nearly half of all adult diffuse gliomas.[1] Contemporary standard-of-care in the postsurgical adjuvant setting for newly diagnosed GBM was established nearly two decades ago by the EORTC-NCIC pivotal phase 3 trial[2,3] that demonstrated improvement in survival with the addition of concomitant oral temozolomide (TMZ) to focal conformal radiotherapy (RT) followed by 6-cycles of adjuvant TMZ (Stupp regimen). However, despite such aggressive multimodality therapy, prognosis remained poor with median survival of 14.6 months, 2-year survival of 27% and 5-year survival <10%.[2,3] The benefit of adding TMZ (concomitant and adjuvant) to RT is largely dependent on O^6-methylguanine DNA methyltransferase (MGMT) gene promoter methylation status[4] which is now an independent prognostic factor as well as predictive marker for response to TMZ.[4,5] In recent times, the addition of tumor-treating fields (TTF) to the Stupp regimen has further improved survival,[6] although not widely available in several parts of the world. Advancements in neuro-surgical adjuncts, modern RT techniques, and aggressive supportive care have provided incremental benefits in outcomes over the last two decades.[7]

There is widespread variability across the globe in the number of adjuvant TMZ cycles[8,9] mostly dictated by prevalent local standards but also based on personal, physician, and institutional biases and preferences. In some healthcare settings, offering 12-cycles of TMZ is quite commonplace; whereas in large parts of the world, TMZ is generally stopped after 6-cycles. Many patients who remain progression free after 6-cycles of TMZ continue to receive further adjuvant TMZ till progression or till 12-cycles (occasionally 24-cycles), or unacceptable toxicity. Many patients with MGMT gene promoter methylation also receive extended adjuvant TMZ (beyond 6-cycles) reflecting the ongoing controversy and debate regarding the most optimal duration of adjuvant TMZ in newly-diagnosed GBM.[8,9]

Two systematic reviews and meta-analyses[10,11] have provided conflicting and contradictory conclusions on the impact of extended adjuvant TMZ in newly diagnosed GBM. The first review[10] pooled data of 1018 patients mostly from retrospective non-randomized comparative studies and reported improvement in survival with extended adjuvant TMZ that can largely be attributed to selection bias inherent to any retrospective analysis. A lack of survival benefit with extended adjuvant TMZ was reported by the second meta-analysis[11] which was restricted only to randomized controlled trials (RCTs) that minimized selection bias. However, total number of patients included in the second meta-analysis[11] restricted to RCTs only was limited (n = 358) with inadequate statistical power resulting in low-certainty of evidence. It is widely accepted that the benefit of adding any TMZ to RT in unmethylated GBM is marginal at best[5] and only patients with methylated tumors may derive benefit if any with extended adjuvant TMZ regimens. Neither of these two systematic reviews and meta-analyses[11,12] provided any subgroup or exploratory analyses based on MGMT gene promoter methylation status due to lack of extractable data from individual primary studies. The objective of this updated systematic review and meta-analysis was to synthesize evidence from all available studies (nonrandomized comparative studies and RCTs) comparing standard 6-cycles of adjuvant TMZ (control arm) versus extended adjuvant TMZ (test arm) in patients with newly diagnosed GBM.

Materials and Methods

This systematic review and meta-analysis was carried out in accordance with Cochrane methodology for systematic reviews of interventional studies[12] and reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] Quality of included primary studies was assessed using Cochrane Risk of Bias tool[14] for RCTs and modified Newcastle-Ottawa scale[15] for nonrandomized comparative studies.

Literature search strategy: A systematic search of medical literature was performed electronically (without language, year, or publication status restrictions) using appropriate keywords such Glioblastoma, GBM, Glioma, High-grade Glioma, HGG; Temozolomide, TMZ, Chemotherapy; Randomized, RCT, Comparative study with Boolean operations (AND, OR) to identify relevant studies comparing the duration of adjuvant TMZ in patients with newly

diagnosed GBM. Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effectiveness (DARE) were also searched. This was further supplemented by hand-searching of review articles, cross references and conference proceedings.

Study eligibility: Any study comparing the duration of adjuvant TMZ in newly diagnosed GBM was considered eligible. This included quasi-randomized studies, propensity-matched analyses, and nonrandomized comparative studies that reported survival outcomes stratified on the number of TMZ cycles as well as RCTs randomly assigning patients to extended (>6-cycles) adjuvant TMZ (test arm) or standard (6-cycles) adjuvant TMZ (control arm). Noncomparative studies or RCTs wherein survival data from control and test arms was either not reported separately or not in extractable format were excluded.

Outcome measures: The primary endpoint of interest was comparative efficacy defined in terms of progression-free survival (PFS) and overall survival (OS). Secondary endpoints included toxicity of adjuvant TMZ. OS was calculated from date of diagnosis (surgery) or date of inclusion in the study and last contact or death from any cause. PFS was calculated from diagnosis or inclusion in the study till documented clinico-radiological progression, last contact, or death whichever occurred earlier. Toxicity outcomes included comparison of TMZ-induced grade 3 or worse myelotoxicity during adjuvant therapy.

Data extraction and statistical analyses: Two reviewers (JMP and AC) independently read each abstract, preprint, publication, protocol, or any other available study report and extracted relevant data from individual primary studies. Any discrepancies were resolved through consensus interpretation by a third reviewer (TG). A standardized format—Participants, Intervention, Comparator, Outcomes (PICO)—was used for data extraction and analysis. Extracted data included study design, patient characteristics, number of participants, details of intervention, comparator details, follow-up duration, survival, and toxicity. Survival outcomes were extracted manually from published Kaplan–Meier (KM) survival curves using WebPlot digitizer.[16] The number of events and the time points (*t*-risk and *n*-risk) were extracted from published data. Standard errors were calculated using the number of events reported in individual primary studies. In case, number of events were not explicitly reported, this was extracted from the reconstructed KM curves. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated using median survival times. HRs (including 95% CIs) from each individual primary study were compared and reconciled with the published values if reported prior to statistical pooling. Grade 3 or worse myelotoxicity comparison between standard adjuvant TMZ and extended adjuvant TMZ was expressed as risk ratio (RR) with 95%CI. All data were pooled using the random-effects model and expressed as HR or RR as appropriate with corresponding 95%CI. Any *p*-value <0.05 was considered as statistically significant. Subgroup analysis was done based on study design (nonrandomized comparative studies versus RCTs) and MGMT gene promoter methylation status (unmethylated versus methylated GBM). Sensitivity analysis (dropping one study at a time) and publication bias (through funnel-plot and Egger's test) were also assessed as appropriate. All analyses were done using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2008), Stata 14.0 (StataCorp LP, TX, USA) and R Studio. Study protocol registered with the International Platform of Registered Systematic Reviews and Meta-analysis Protocols (INPLASY2021120114) in 2021 was revised for updated evidence-synthesis. No source of funding was involved in data extraction, analysis, interpretation, or reporting of results.

Results

The PRISMA flow-diagram of study selection and inclusion in this systematic review and meta-analysis is depicted in Figure 1 with detailed PRISMA check-list as online Supplementary File S1. Comprehensive and systematic search of the scientific literature identified a total of 294 potentially eligible records that were retrieved for further review. After removing duplicates, inappropriate, or irrelevant reports (n = 77), 217 abstracts were screened of which 176 records were excluded leaving 41 abstracts for consideration of inclusion in the meta-analysis. Studies where survival data could not be reliably extracted for control and test arms separately, review articles, letters, and editorials were further excluded leaving 21 primary studies for inclusion. There were 16 nonrandomized comparative studies[17–32] and 5 RCTs[33–37] involving a total of 2578 patients (1342 in the standard adjuvant TMZ arm and 1236 patients in extended adjuvant TMZ arm) that were finally included for updated evidence-synthesis. Baseline study characteristics and survival outcomes of nonrandomized comparative studies and RCTs are summarized in Tables 1 and 2, respectively.

Evidence synthesis: RCTs were considered to have low, unclear, or high risk of bias according to assessment on the following items: random sequence generation and concealment of allocation (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessors (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and any other sources of bias that could influence the quality of the study. All included RCTs was rated generally as good with low risk of bias for survival outcomes excepting for a single RCT with unclear risk of bias (as it was reported only in abstract form). Quality of nonrandomized comparative studies was rated as moderate to poor (class III-IV evidence) on the modified Newcastle-Ottawa scale (online Supplementary File S2) based on identified selection, performance, attrition, and reporting biases. Extended adjuvant TMZ was associated with statistically significant reduction in the risk of progression (HR = 0.72, 95%CI: 0.60–0.87; p = 0.007) (Figure 2) and death (HR = 0.71, 95%CI: 0.57–0.90; p = 0.004) (Figure 3) compared to standard adjuvant TMZ. Subgroup analysis based on study design however showed that the beneficial impact of extended adjuvant TMZ was largely driven by nonrandomized comparative studies both for PFS (HR =

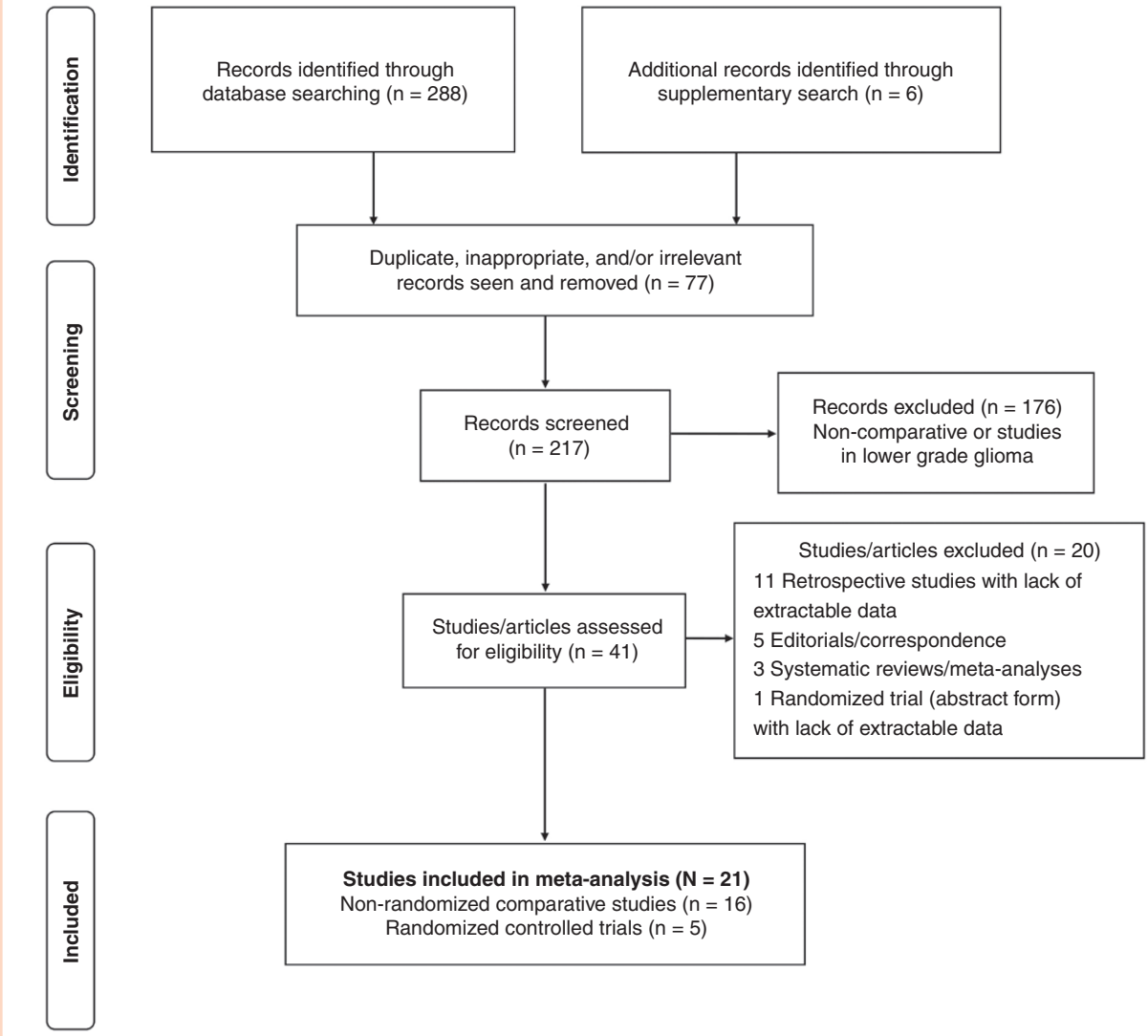

Figure 1. PRISMA flow-diagram of study selection and inclusion in the meta-analysis.

0.68, 95%CI: 0.54–0.86; $p = 0.001$) and OS (HR = 0.67, 95%CI: 0.51–0.89; $p = 0.005$). There was no statistically significant improvement in PFS (HR = 0.86, 95%CI: 0.65–1.14; $p = 0.29$) or OS (HR = 0.90, 95%CI: 0.65–1.25; $p = 0.54$) with extended adjuvant TMZ for patients enrolled in RCTs wherein selection bias is minimized due to random assignment to the treatment arms with allocation concealment. Subgroup analysis based on MGMT methylation status could not be done due to lack of extractable data. Similarly, lack of granular data on myelotoxicity during adjuvant TMZ in most retrospective studies precluded pooling of toxicity outcomes. Sensitivity analysis (Figure 4) demonstrated lack of influence of any single study on the overall treatment effect, inferences, and conclusions. Slight asymmetry in the funnel-plot (Figure 5) suggested that publication bias could not be completely ruled out. Egger's test, however, demonstrated lack of any significant publication bias for PFS ($p = 0.44$) and OS ($p = 0.28$) in this updated systematic review and meta-analysis (Figure 5).

Discussion

Contemporary postsurgical standard-of-care in patients with newly-diagnosed GBM comprising of focal conformal RT with concomitant TMZ followed by 6-cycles of adjuvant TMZ (Stupp regimen) was established by the EORTC-NCIC pivotal phase 3 trial[2,3] nearly two decades ago. Ever since, the impact of extended adjuvant TMZ (beyond 6-cycles) on survival outcomes has remained controversial with no consensus on the optimal duration of adjuvant TMZ.[8,9] The availability of MGMT gene promoter methylation as a predictive marker of response to alkylating TMZ chemotherapy and lack of cumulative toxicity with TMZ has prompted several oncologists to continue adjuvant TMZ based on local standards and personal/institutional preferences beyond 6-cycles (till 12-cycles, occasionally 24-cycles) or until documented progression or unacceptable toxicity in diverse

Table 1. Baseline characteristics, study quality, and summary survival outcomes of non-randomized comparative studies of standard adjuvant TMZ (6-cycles) versus extended adjuvant TMZ (>6-cycles) in patients with newly-diagnosed GBM

Author[ref]	Age range (years)	Males (%)	RT dose	Median FU (months)	Study quality	Treatment arm	No. of patients	Median PFS (months)	Median OS (months)
Attia[17]	25–68 years	74.5%	60Gy	20	Class IV	6-cycles TMZ	29	15	18
						>6-cycles TMZ	26	18	22
Barbagallo[18]	30–82 years	51.3%	60Gy	NA/NR	Class IV	6-cycles TMZ	18	4	8
						>6-cycles TMZ	19	20	28
Blumenthal[19]	18–70 years	56.6%	60Gy	NA/NR	Class III	6-cycles TMZ	333	10.4	24.9
						>6-cycles TMZ	291	12.2	27
Chen[20]	NA/NR	52.5%	60 Gy	NA/NR	Class III	6-cycles TMZ	40	16.7	9.6
						>6-cycles TMZ	53	29	13.8
Darlix[21]	18–76 years	65.5%	60 Gy (55–66)	NA/NR	Class IV	6-cycles TMZ	30	18	28.2
						>6-cycles TMZ	28	27	30
Elsaka[22]	46–62 years	62.8%	≥50 Gy	NA/NR	Class IV	6-cycles TMZ	74	9.67	12.53
						>6-cycles TMZ	31	22.9	27.33
Gherasim-Morogai[23]	20–80 years	54%	60 Gy	16	Class IV	6-cycles TMZ	85	10	20
						>6-cycles TMZ	42	20	29
Gramatzki[24]	23–74 years	58%	NA/NR	77	Class III	6-cycles TMZ	81	17.18	33.2
						>6-cycles TMZ	61	20.49	32.6
Heish[25]	25–71 years	71%	60 Gy	NA/NR	Class IV	6-cycles TMZ	7	17	30.9
						>6-cycles TMZ	7	43.4	48.4
Huang[26]	NA/NR	56.6%	60 Gy	6.5	Class IV	6-cycles TMZ	27	15	19.4
						>6-cycles TMZ	26	20.1	25.6
Karadag[27]	18–76 years	55.8%	60 Gy	NA/NR	Class IV	6-cycles TMZ	43	16	24
						>6-cycles TMZ	30	14	22
Quan[28]	18–70 years	52%	60 Gy	NA/NR	Class IV	6-cycles TMZ	55	14.2	20.6
						>6-cycles TMZ	20	17	47
Skardelly[29]	NA/NR	NA/NR	NA/NR	NA/NR	Class IV	6-cycles TMZ	64	10.9	18.9
						>6-cycles TMZ	43	20.9	28.6
Urgoiti[30]	22–86 years	63%	NA/NR	NA/NR	Class IV	6-cycles TMZ	23	12	16.5
						>6-cycles TMZ	29	15	24.6
Villegas-Mejía[31]	NA/NR	55%	60 Gy	NA/NR	Class IV	6-cycles TMZ	84	NA	15
						>6-cycles TMZ	109	NA	46
Wang[32]	NA/NR	54.6%	60 Gy	36.5	Class IV	6-cycles TMZ	123	12	13
						>6-cycles TMZ	183	20	36

TMZ, temozolomide; RT, radiotherapy; GBM, glioblastoma; PFS, progression-free survival; OS, overall survival; NA/NR, not available/not reported.

healthcare settings across the world without solid scientific evidence.

There are conflicting reports on the efficacy of extended adjuvant TMZ in patients with newly diagnosed GBM that have been the subject of evidence-synthesis in two prior systematic reviews and meta-analysis. The first such systematic review and meta-analysis[10] pooled data from 1018 glioblastoma patients enrolled in 7 comparative studies including secondary analysis of Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) trial database, post hoc analysis of the German Glioma Network registry data, three retrospective studies and two small RCTs. The authors reported significant improvement in PFS (difference in means $Z = 3.84$ months, 95%CI: 2.559–7894; $p < 0.001$) and OS (difference in means $Z = 2.375$ months, 95%CI: 1.002–10.467; $p = 0.18$) with extended adjuvant TMZ (>6-cycles) compared to standard (6-cycles) adjuvant TMZ. However, authors also acknowledged methodological limitations of their meta-analysis warranting cautious interpretation of the findings given the potential for significant selection bias given that majority of pooled data was derived from retrospective studies. More recently, another systematic review and meta-analysis[11] pooled data from 358 patients

Table 2. Baseline characteristics, risk of bias, and summary survival outcomes of randomized controlled trials comparing standard adjuvant TMZ (6-cycles) versus extended adjuvant TMZ (>6-cycles) in patients with newly diagnosed GBM

Author[ref]	Age range (years)	Males (%)	RT dose	Median FU (months)	Risk of bias	Treatment arm	No. of patients	Median PFS (months)	Median OS (months)
Balana[$#33]	29–83 years	52.2%	NA/NR	33.4	Low	6-cycles TMZ	79	7.7	23.3
						>6-cycles TMZ	80	9.5	18.2
Bhandari[34]	19–65 years	60%	60 Gy	17.3	Low	6-cycles TMZ	20	12.8	15.4
						>6-cycles TMZ	20	16.8	23.8
Elsebai[35]	18–65 years	55%	60 Gy	NA/NR	Low	6-cycles TMZ	20	5.6	10.8
						>6-cycles TMZ	20	7.3	12.4
Javadinia[36]	≥18 years	NA/NR	NA/NR	16.5	Unclear	6-cycles TMZ	50	11.3	20.2
						>6-cycles TMZ	50	13.0	23.2
Refae[37]	19–72 years	79.7%	59 Gy	15.2	Low	6-cycles TMZ	29	10.4	14.1
						>6-cycles TMZ	30	13.2	18.8

TMZ, temozolomide; RT, radiotherapy; GBM, glioblastoma; PFS, progression-free survival; OS, overall survival; NA/NR, not available/not reported.
$Survival outcomes were reported from date of inclusion in the study (after 6-cycles TMZ) and not from date of diagnosis (surgery).
#Updated results (at ASCO 2021) reported median OS of 22.0 months in control arm (6-cycles TMZ) and 18.2 months in experimental arm (>6-cycles TMZ).

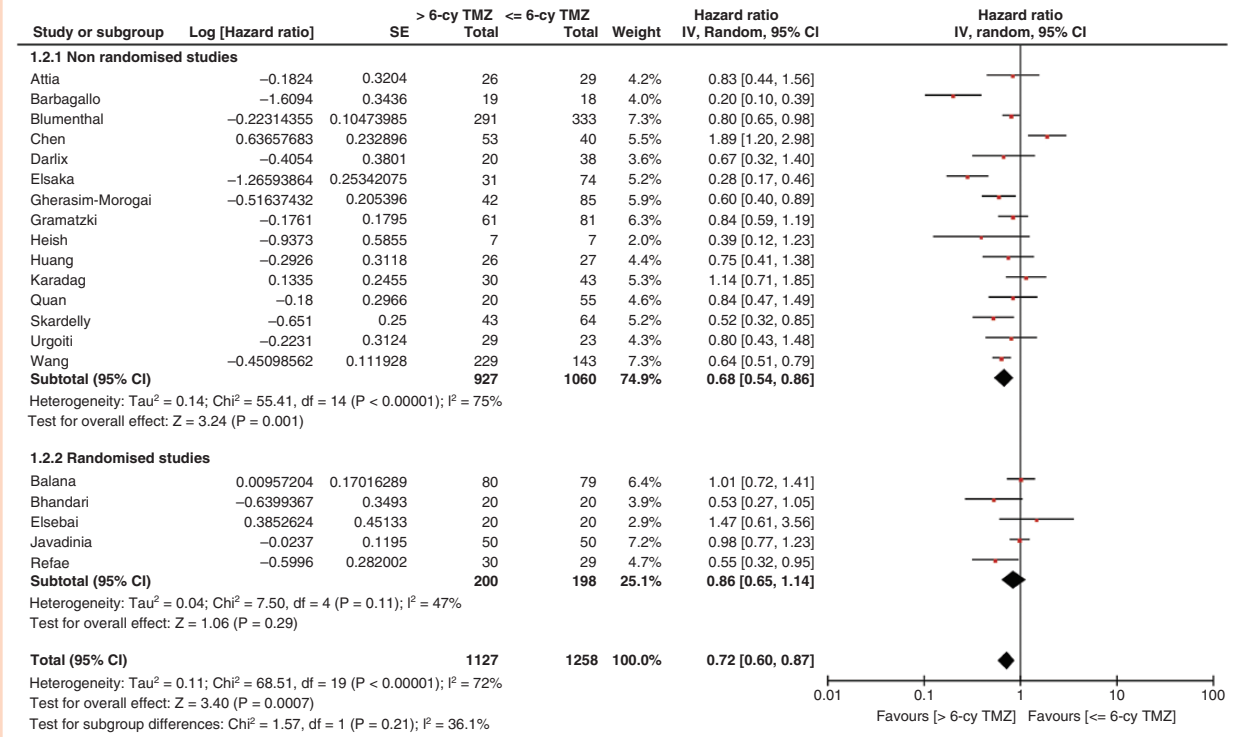

Figure 2. Forest plots demonstrating progression-free survival (PFS) in nonrandomized comparative studies and randomized controlled trials comparing standard adjuvant temozolomide (6-cycles) versus extended adjuvant temozolomide (>6-cycles) in patients with newly-diagnosed glioblastoma.

that had been enrolled in 4 RCTs comparing standard adjuvant TMZ to extended adjuvant TMZ to minimize selection bias. The authors reported no significant improvement in PFS (HR = 0.82, 95%CI: 0.61–1.10; $p = 0.18$) or OS (HR = 0.87, 95%CI: 0.60–1.27; $p = 0.48$) with extended adjuvant TMZ compared to standard adjuvant TMZ. The rates of grade 3 myelotoxicity though somewhat higher with extended adjuvant TMZ were not significantly different between the two arms. The authors concluded that there is low-certainty evidence that extended adjuvant TMZ is not associated with

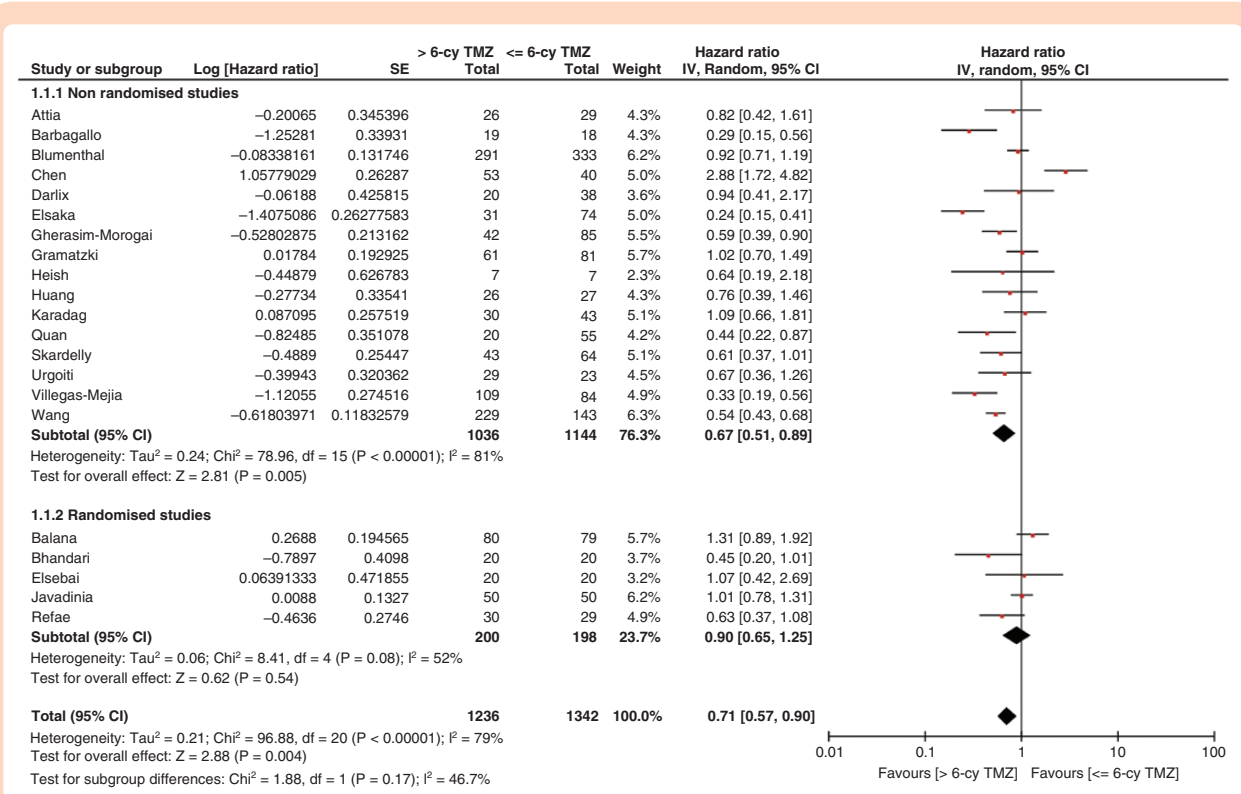

Figure 3. Forest plots demonstrating overall survival (OS) in nonrandomized comparative studies and randomized controlled trials comparing standard adjuvant temozolomide (6-cycles) versus extended adjuvant temozolomide (>6-cycles) in patients with newly diagnosed glioblastoma.

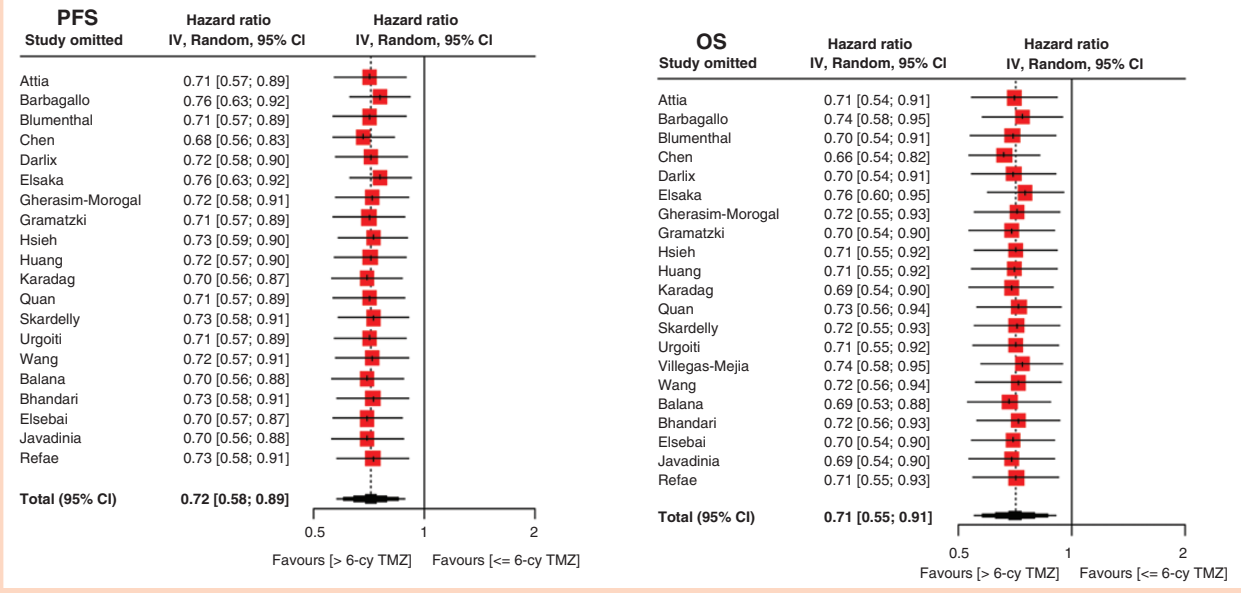

Figure 4. Sensitivity analysis demonstrating the lack of influence of any single study on progression-free survival (PFS) and overall survival (OS) in the systematic review and meta-analysis comparing standard adjuvant temozolomide (6-cycles) versus extended adjuvant temozolomide (>6-cycles) in patients with newly-diagnosed glioblastoma.

significant benefits or harms in unselected patients with newly diagnosed GBM and should not be offered outside the context of prospective clinical trials.

This updated systematic review and meta-analysis pools data from all available comparative studies (both nonrandomized as well as RCTs) to generate the largest

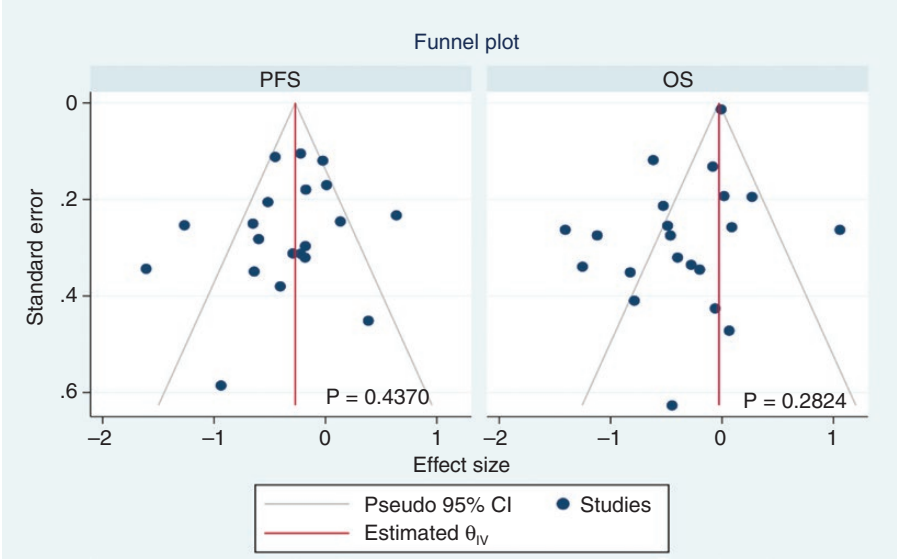

Figure 5. Mild asymmetry in the funnel-plot for progression-free survival (PFS) and overall survival (OS) indicating that publication bias could not be ruled out. Egger's test, however, demonstrated lack of any significant publication bias in the systematic review and meta-analysis comparing standard adjuvant temozolomide (6-cycles) versus extended adjuvant temozolomide (>6-cycles) in patients with newly-diagnosed glioblastoma.

evidence-base assessing the impact of extended adjuvant TMZ in patients with newly diagnosed GBM. The level of evidence generated from any meta-analysis depends upon the source material including quality of primary studies. It is widely accepted that nonrandomized studies tend to overestimate treatment effects and can often be misleading. Apparent benefit of continuing TMZ beyond the standard 6-cycles was evident on pooling data from nonrandomized comparative studies with inherent potential for selection bias. Nonrandomized comparative studies included in this updated meta-analysis were of moderate to poor quality resulting in low level of evidence. Such benefit was not seen when evidence-synthesis was based on patients enrolled in prospective RCTs wherein the process of randomization minimizes various known and unknown biases including selection bias. Although included RCTs were of high-quality, most of them were underpowered, single institution studies with limited patient numbers limiting applicability and generalizability. It has been recently recognized that majority of clinical trials[38,39] in neuro-oncology including GBM have been suboptimal needing more careful consideration. Assuming 10% improvement in 2-year OS from 30% to 40% (HR = 0.76) with extended adjuvant TMZ (superiority hypothesis) in unselected newly diagnosed GBM, a total 600 patients would need to be randomized (300 in each arm) accounting for 10% attrition rate with 80% power at the 0.05 significance level. It is pertinent to note that the total number of patients randomized in the 5 RCTs included in this updated meta-analysis was limited (n = 398) resulting in low power to demonstrate significant benefit if any. If the real benefit of extended adjuvant TMZ was largely restricted to patients with methylation of the MGMT gene promoter, an even larger sample size (over 1000 patients) would be required to draw any meaningful conclusions.

A better understanding of disease biology suggests that possibly patients with methylation of the MGMT gene promoter could benefit with continuation of TMZ beyond 6-cycles.[4,5] Conversely, patients with unmethylated MGMT are likely to derive little benefit, if any, even with the standard 6-cycles,[4,5] let alone extended adjuvant TMZ. The practice of extending the duration of adjuvant TMZ in methylated GBM is quite empirical without any real or conclusive evidence. Proponents of this approach cite the lack of other effective treatment options, ease of oral administration, and no significant cumulative toxicity of TMZ. On the other hand, critics of extended adjuvant treatment regimen point toward the inherently better prognosis of methylated tumors (with resultant longer PFS and OS) that allows patients to continue to receive adjuvant TMZ beyond the standard 6-cycles without necessarily impacting upon survival. Secondary analysis of the RTOG/EORTC dataset[19] stratified on MGMT gene promoter methylation status showed modest PFS benefit of extended adjuvant TMZ in the methylated cohort (HR = 0.65, 95%CI: 0.50–0.85; p = 0.019) which was lost in the unmethylated subset (HR = 0.88, 95%CI: 0.64–1.21; p = 0.43). However, there was no significant difference in OS with extended adjuvant TMZ regardless of MGMT methylation. More recently, no significant survival benefit (PFS and OS) of extended adjuvant TMZ was reported in the largest RCT[33] even in patients with methylated MGMT raising question marks on offering TMZ beyond 6-cycles in routine clinical practice. It is conceivable that prolonged exposure to TMZ (beyond 6-cycles) could actually be counterproductive due to the development of aggressive clones and hypermutator phenotype with consequent resistance to alkylating chemotherapy during salvage treatment for recurrent/progressive disease that may negate any purported PFS benefit seen at initial diagnosis. Further exploratory analysis based on MGMT gene promoter methylation status would be hypothesis-generating for testing the extended adjuvant TMZ paradigm in a biomarker-enriched (methylated) cohort. Two ongoing Australian trials EX-TEM (ACTRN12618001944224)[40] and

MAGMA (ACTRN12620000048987)[41] are currently testing the safety and efficacy of extended adjuvant TMZ in patients with newly diagnosed GBM using MGMT status for stratification. Biomarker-based Optimization of Adjuvant Therapy (BOAT) study is the only prospective study (CTRI/2018/11/016349) that is randomly assigning GBM patients with methylated MGMT to standard 6-cycles of TMZ versus extended adjuvant TMZ.[42]

Strengths and limitations: This report represents the largest cohort of patients (n=2578) whose data has been pooled in any systematic review and meta-analysis assessing the impact of extended adjuvant TMZ in newly-diagnosed GBM. Another strength of the meta-analysis lies in reconstruction of the published KM curves for extraction of data and use of modern meta-analytical methods for statistical pooling. Despite the above strengths, several caveats and limitations remain. Apart from pooling data from prospective RCTs, this meta-analysis also included nonrandomized comparative studies with inherent selection and performance bias leading to substantial downgrading of evidence. Subgroup analysis based on MGMT gene promoter methylation status could not be done due to lack of extractable data in individual primary studies. Influence of other covariates such as age (young vs elderly) and gender (male vs female) could not be assessed due to lack of granular data in primary studies. The synthesis of evidence was primarily based on published reports without access to individual participant data from the included studies. Finally, this meta-analysis did not study the cost-effectiveness of extended adjuvant TMZ including its impact on patient's health-related quality of life.

Conclusions

Apparent survival benefit of extended adjuvant TMZ in newly diagnosed GBM is largely driven by nonrandomized comparative studies with high inherent potential for multiple biases, some of which can be minimized through randomization. Results from ongoing large RCTs are likely to provide high-quality evidence regarding the optimal duration of adjuvant TMZ in the future.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* online.

Keywords:

adjuvant | bias | extended | glioblastoma | meta-analysis | temozolomide

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Conflict of Interest Statement

None of the authors have any conflicts of interest to declare.

Authorship Statement

Study concept, design, and supervision: Tejpal Gupta. Literature search: Jeevi Mona Priyadharshni Selvarajan, Archya Dasgupta, Tejpal Gupta. Screening records and data extraction: Jeevi Mona Priyadharshini Selvarajan, Abhishek Chatterjee. Statistical analysis: Sadhana Kannan, Tejpal Gupta. Manuscript writing: first draft- Jeevi Mona Priyadarshni Selvarajan, final draft- Tejpal Gupta. Critical review and editing of manuscript: Nandini Menon, Abhishek Chatterjee. Final approval of manuscript: All authors.

Data Sharing

All extracted data from individual primary studies is vested with the Principal Investigator and corresponding author that can be made available on reasonable request.

Institutional Ethics Committee Approval

Not applicable.

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