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CLINICAL STUDY

Optimal adjuvant therapy in elderly glioblastoma: results from a systematic review and network meta-analysis

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Abstract

Background There exists lack of consensus worldwide regarding the most optimal adjuvant therapy regimen in elderly patients with newly-diagnosed glioblastoma (GBM).

Purpose To identify the most optimal adjuvant therapy regimen in elderly GBM patients through systematic review and network meta-analysis.

Methods Prospective trials randomly assigning elderly GBM patients post-operatively to any adjuvant therapy regimen were included. The primary outcome measure was overall survival. Numbers of events, patients at-risk, and censored patients for survival were estimated from Kaplan–Meier survival curves in the interval of 0–12 months. The total person-time at risk and the mortality × 100 person-months was also estimated. The relative ranking probability of each treatment and rankograms were used to estimate the hierarchy of each intervention in terms of overall survival. The mean rank values and the surface under the cumulative ranking (SUCRA) curves were also calculated.

Results A systematic literature search identified 1278 abstracts, that were screened to retrieve full-text manuscripts of potentially eligible articles. After detailed assessment, data from 1569 patients in 7 randomized controlled trials (RCTs) treated with one of following regimens was extracted and analyzed: normofractionated radiotherapy (RT) delivered over 5.5–6 weeks; moderately hypofractionated RT (2–3 weeks) either alone or in combination with temozolomide or bevacizumab; extremely hypofractionated RT (1-week); temozolomide monotherapy; and best supportive care alone. In terms of overall survival, moderately hypofractionated RT (3-weeks) with concurrent and adjuvant temozolomide emerged as the best and second-best adjuvant therapy option with 81% probability and 99.1% probability respectively. Using SUCRA, the surface area for moderately hypofractionated RT (3-weeks) with concurrent and adjuvant temozolomide reached almost 100%, confirming it as the best intervention. As expected, best supportive care alone was ranked as the worst treatment strategy.

Conclusion Moderately hypofractionated RT (3-weeks) with concurrent and adjuvant temozolomide is the most optimal and preferred adjuvant therapeutic regimen in elderly GBM.

Keywords Adjuvant · Elderly · Glioblastoma · Meta-analysis · radiotherapy · Temozolomide

Introduction

Glioblastoma (GBM) is the most common malignant primary tumor of the central nervous system (CNS) in adults comprising nearly 40% of all primary brain tumors [1]. As per data from the Central Brain Tumor Registry of United States (CBTRUS), median age at diagnosis for GBM is presently around 64 years [1] with an increasing incidence due to ageing. The contemporary standard of care for newly-diagnosed GBM is maximal safe neurosurgical resection and post-operative focal conformal radiotherapy (RT) to the tumor bed with margins using conventional fractionation (1.8–2 Gy per fraction for a

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total dose of 59.4–60 Gy in 30–33 fractions delivered over 6–6.5 weeks) with concurrent oral temozolomide chemotherapy (75 mg/m^2) followed by six cycles of adjuvant temozolomide chemotherapy (150–200 mg/m^2 D1–D5 every 4-weekly). Despite such multi-modality management, the prognosis of patients with GBM remains poor worldwide with an expected median survival of 15 months, 2-year survival of 27%, and 5-year survival barely reaching 10% [2, 3]. The survival outcomes decrease significantly with increasing age as exemplified by 1-year and 2-year relative survival of 40% and 14% for patients aged between 55 and 64 years which falls sharply to around 13% and 4% for patients ≥ 70 years at index diagnosis [4, 5]. The management of elderly GBM poses unique challenges due to limited life-expectancy (median survival around 6-months), existing multiple co-morbidities, and increased risk of treatment-related toxicity on the ageing brain [5, 6].

Several adjuvant therapy regimens have been tested in the elderly population in randomized controlled trials (RCTs) across the world; however most elderly patients with newly-diagnosed GBM still continue to be treated on personal, physician, and institutional biases and preferences with significant cost and resource implications. Prior systematic reviews and meta-analyses in elderly GBM [7–9] have inappropriately pooled data from different types of study designs (retrospective analyses, uncontrolled prospective trials, registry data, and RCTs) with high-risk of biased interpretation and reporting. Synthesis of evidence regarding the most optimal adjuvant therapy regimen in elderly GBM using traditional meta-analytic methods is therefore a difficult and challenging task. Although various adjuvant therapeutic options have been compared in RCTs in elderly GBM, lack of head-to-head trials makes direct comparisons of certain treatments impossible. The use of different measures of survival across trials further confounds extraction and interpretation. Frequentist or classical approach to network meta-analysis (NMA) also known as mixed treatment comparison is a potential solution to these problems [10]. The use of NMA enables indirect comparison using a common comparator when a head-to-head trial is not available and combines direct and indirect comparisons to simultaneously compare several treatments while preserving the virtues of randomization in individual trials.

Aims and objectives

The aim of this study was to identify the most optimal adjuvant therapy regimen in elderly patients with newly-diagnosed GBM patients through a systematic review and NMA of prospective RCTs.

Materials and methods

This systematic review and NMA was carried out in accordance with Cochrane methodology [11] including quality assessment of individual studies using the Cochrane risk of bias method [12] and reported using the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Literature search strategy

Eligible studies directly comparing post-operative adjuvant therapy regimens in elderly patients with newly-diagnosed GBM were identified through a systematic search of the medical literature using a validated search strategy. An electronic search of Medline via PubMed was conducted from January 1995 onwards till November 2018 restricted to the English language using the terms “astrocytoma OR Glioblastoma OR glioma” AND "Randomized Clinical Trial" OR randomised OR randomized AND "Radiation Therapy" OR radiotherapy OR chemotherapy OR temozolomide OR “targeted therapy” OR bevacizumab OR hypofractionated OR “best supportive care”. The Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effectiveness (DARE) were also searched electronically from inception till December 2018. Electronic search was further supplemented by hand-searching of review articles, cross references and conference proceedings.

Study selection

Only prospective RCTs randomly assigning elderly patients with histo-pathologically proven newly-diagnosed GBM to post-operative adjuvant therapy were included, provided there was a comparator arm that was not confounded by additional differences between the two groups. The definition of elderly was somewhat arbitrary and variable across the included studies with age cut-offs ranging from 60 years and above to ≥ 70 years.

Data extraction and assessment for risk of bias

Two reviewers (BK, SK) independently reviewed full-text manuscripts of all eligible studies and extracted relevant data and information regarding Population (patient demographics, study-level inclusion and exclusion criteria); Interventions (treatment regimen of test arms); Comparisons (treatment regimen of comparator arms); and Outcomes (survival) – PICO format. The analysis, interpretation, and reporting of results also included a risk of bias assessment for all included individual studies. Any discrepancy in data extraction and/

or disagreement in risk of bias was resolved by the third reviewer (TG) through joint review of the manuscripts to reach consensus.

Data synthesis and analysis

The primary outcome measure was overall survival (OS) as it is the most relevant and hardest end-point not influenced by any salvage therapy. Other endpoints included in the systematic review, but not pooled in the NMA were progression-free survival (PFS), toxicity including neuro-cognitive impairment, and quality-of life (QOL). Before pooling the data in the network, a pair-wise comparison of different interventions from all studies was conducted similar to a conventional meta-analysis. The hazard ratio (HR) for death for such pair-wise comparison was computed using the fixed-effects model and reported as point estimate along with 95% credible intervals (CrIs). Numbers of events, patients at-risk, and censored patients for survival were estimated from Kaplan–Meier survival curves in the interval of 0–12 months, using appropriate methodology. The total person-time at risk and the mortality × 100 person-months was estimated. The network was also checked for inconsistency to assess when the direct comparison of one treatment versus another one, derived from one or more studies included in NMA, conflicts with evidence drawn via the indirect comparison estimated through the NMA. The restricted maximum likelihood method was used to estimate heterogeneity, assuming a common variance estimate across different comparisons for each single outcome considered. A frequentist approach of NMA was used to compare available treatment strategies within a single analytical framework. Potential publication bias was evaluated through a funnel plot. NMA was performed with Stata 14.0 (StataCorp, College Station, TX, USA) using the 'network' command and routines [14]. The relative ranking probability of each treatment and rankograms were used to estimate the hierarchy of each intervention in terms of patient survival. The mean rank values and the surface under the cumulative ranking (SUCRA) curves were also calculated. SUCRA is a graphical representation of the overall ranking generally denoted as a single number associated with each treatment, with value range from 0 to 100%. Higher the SUCRA value for any treatment and closer to 100%, greater the likelihood of that particular treatment being the top-ranked or one of the top-ranked treatments. Lower the SUCRA value of any treatment and closer to 0, more likely it would be one of the bottom-most treatments.

Results

The flow-diagram of study selection and inclusion in the NMA is depicted in Fig. 1. The detailed PRISMA check-list is also provided in online supplementary file S1. Systematic search of the indexed medical literature identified 1278 abstracts, which were screened to retrieve full-text manuscripts of potentially eligible articles. After rigorous and detailed assessment, inappropriate, irrelevant, and duplicate records were excluded leaving eight publications [15–22] corresponding to 7 primary RCTs that were finally included in the network. One multicentric RCT [23] randomly assigning patients to moderately hypofractionated RT (n = 14) versus temozolomide monotherapy (n = 17) though originally designed for the elderly (> 65 years) and frail patients i.e. Recursive Partitioning Analysis (RPA) classes V and VI was later amended to include younger patients (< 65 but > 50 years of age), provided they belonged to same RPA class (V or VI). This study was not included in the network as the survival outcomes of elderly patients were neither reported separately nor extractable from the published report.

Overview of included studies

All included studies were prospective RCTs randomly assigning elderly patients with newly-diagnosed GBM to post-operative adjuvant therapy. Data from 1569 patients in these seven primary RCTs randomized to one of the following adjuvant therapy regimens was extracted and analyzed: normofractionated RT (5.5–6 weeks); moderately hypofractionated RT (2–3 weeks) either alone or in combination with temozolomide or bevacizumab; extremely hypofractionated RT (1-week); temozolomide monotherapy; and best supportive care alone. Six trials compared 2 interventions only, while one was a 3-arm trial [17]. All studies had an active comparator, excepting a single study that used best supportive care alone [16] as the comparator arm. Three trials each used a non-inferiority [15, 18, 21] and superiority design [16, 17, 19] while one trial though randomized used a non-comparative design [22]. One primary trial originally included elderly and/or frail patients in the main analysis [20], but separately reported outcomes of the elderly cohort (≥ 65 years) as subset analysis in a companion publication [21], data from which was included in the meta-analysis. Although participants or physicians were not blinded in any of the trials, quality of individual studies was generally high. Six index RCTs [15–19, 22] demonstrated a low-risk of bias for survival outcomes, while the separately reported subset analysis [21] of a larger RCT was associated with an uncertain risk of bias (online supplementary file S2). Characteristics of included RCTs and survival outcomes are summarized in Tables 1 and 2 respectively.

Data synthesis

The network diagram (Fig. 2) represents the comparisons between the various treatment arms with the maximum

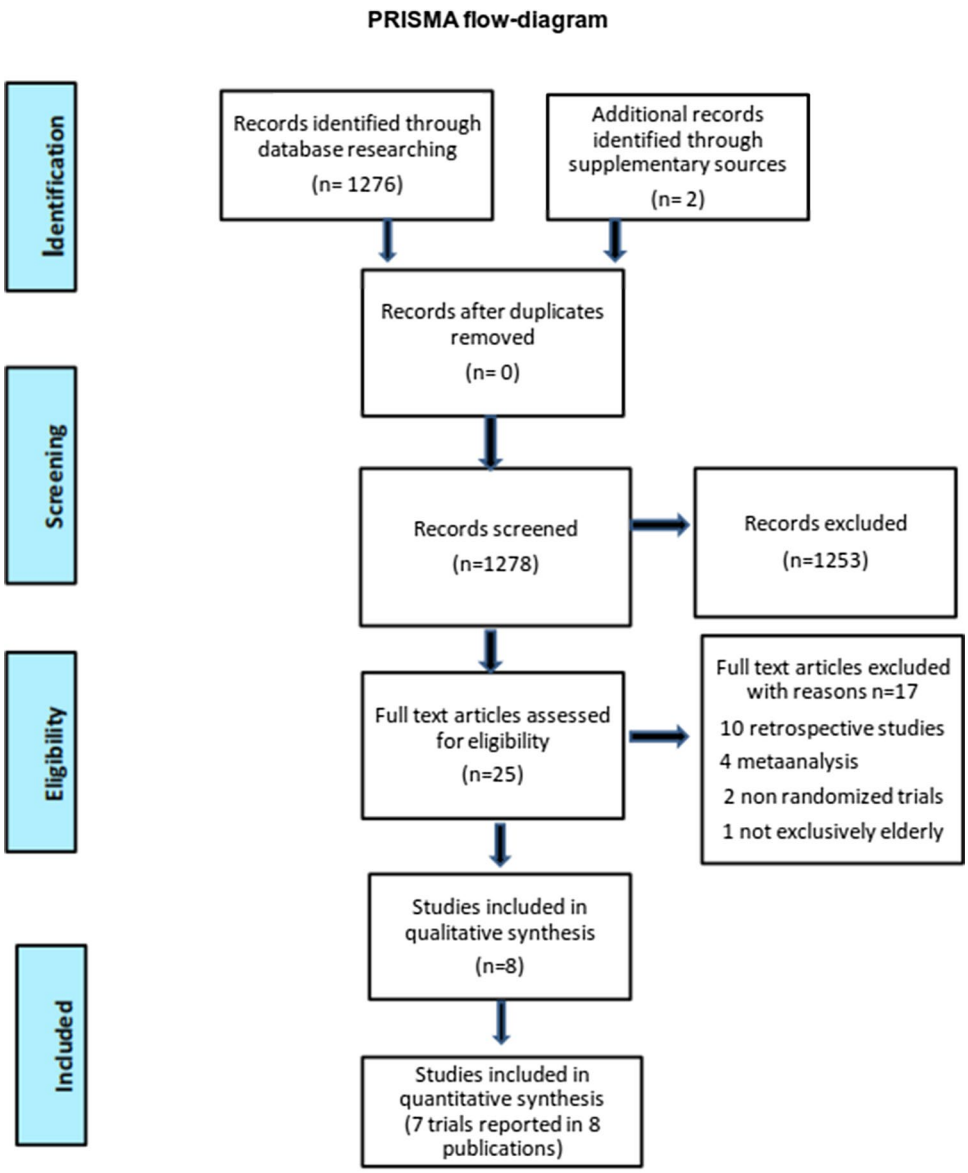

Fig. 1 Flow-diagram of study selection and inclusion in the systematic review and meta-analyses as per PRISMA guidelines

number of patients (n = 592) being compared between normofractionated RT versus temozolomide monotherapy across two studies [17, 18]. The second largest comparison (n = 542) was between hypofractionated RT versus hypofractionated RT plus temozolomide in one study [19], followed by the comparison (n = 318) between normofractionated RT versus moderately hypofractionated RT (2–3 weeks) across two studies [15, 17]. Best supportive care alone [16], extremely hypofractionated RT [21], and hypofractionated RT plus bevacizumab [22] were the regimens with least representation in the network. Point estimates of the HR with 95% CrIs computed using the fixed-effects model for the pair-wise comparison of different interventions across all studies is presented in Fig. 3.

In terms of overall survival, moderately hypofractionated RT (3-weeks) with concurrent and adjuvant temozolomide emerged as the best and second-best adjuvant therapy option with 81% probability and 99.1% probability respectively (Table 3). Using SUCRA, the surface area for moderately hypofractionated RT (3-weeks) with concurrent and adjuvant temozolomide reached almost 100%, confirming it as the best intervention (Fig. 4). According to the rankogram, extremely hypofractionated RT (25 Gy in 5 fractions over 1 week) emerged as the second-best adjuvant treatment regimen with a 65.3% probability (Table 3). This finding, however, needs to be interpreted cautiously in the context of small number of patients (n = 26) treated with such extreme hypofractionation included in the network as well as inherent bias in any post-hoc subset analysis. As expected, best supportive care alone was ranked as the worst treatment strategy in terms of overall survival (Fig. 4). No significant heterogeneity or inconsistency was detected in the network

Table 1 Patient and treatment characteristics of individual randomized controlled trials in elderly patients with newly-diagnosed glioblastoma included in the network meta-analysis

Study-year (ref)	Treatment arms	RT dose and fractionation	Number of pts (N)	Age cut-off (years)	Median age (years)	Median KPS	Patients with GTR/STR (%)	Steroids at start (%)
Roa 2004 [15]	Normofractionated RT (6-wk RT)	60 Gy/30#/6-wk	47	≥ 60	72.4	70	56.5	NA
	Hypofractionated RT (3-wk RT)	40 Gy/15#/3-wk	48		71	70	64.6	NA
Guibert 2007 [16]	Normofractionated RT (5.5-wk RT)	50 Gy/28#/5.5-wk	39	≥ 70	75	70	48.7	82
	Best supportive care alone	Not applicable	42		73	70	47.6	86
Malmstrom 2012 [17]	TMZ monotherapy	Not applicable	119	> 60	70	90	74	51
	Hypofractionated RT (2-wk RT)	34 Gy/10#/2-wk	123		70	90	73	51
	Normofractionated RT (6-wk RT)	60 Gy/30#/6-wk	100		70	90	73	56
Wick 2012 [18]	TMZ monotherapy	Not applicable	195	> 65	72	70	53.3	18
	Normofractionated RT (6-wk RT)	60 Gy/30#/6-wk	178		71	80	51.3	28
Perry 2017 [19]	Hypofractionated RT (3-wk RT)	40 Gy/15#/3-wk	271	≥ 65	73	90	68.3	23.8
	Hypofractionated RT (3-wk RT) + TMZ	40 Gy/15#/3-wk	271		73	90	68.3	25.6
de Castro 2017 [21]	Hypofractionated RT (3-wk RT)	40 Gy/15#/3-wk	35	≥ 65	NA	60	77.1	42
	Extremely hypofractionated RT (1-wk RT)	25 Gy/5#/1-wk	26		NA	60	84.6	48
Wirsching 2018 [22]	Hypofractionated RT (3-wk RT) + BEV	40 Gy/15#/3-wk	50	≥ 65	70	90	NA	44
	Hypofractionated RT (3-wk RT)	40 Gy/15#/3-wk	25		70	90	NA	44

RT radiotherapy, *pts* patients, *KPS* Karnofsky performance status, *GTR* gross total resection, *STR* subtotal resection, # fractions, *wk* week, *TMZ* temozolomide, *BEV* bevacizumab, *NA* not available

and a relatively symmetric funnel-plot (online supplementary file S3) denoted the lack of potential publication bias. Quantitative data synthesis for PFS was not performed in the NMA. However, from reported data in individual studies, it was evident that moderately hypofractionated RT combined with either temozolomide or bevacizumab resulted in best 6-month PFS while best supportive care alone was associated with worst outcomes. Lack of uniform reporting of toxicity and QOL outcomes in the primary RCTs precluded statistical pooling of such data in the meta-analysis.

Discussion

There exists a lack of consensus worldwide regarding the most optimal approach to treating elderly patients with newly-diagnosed GBM [24, 25], who continue to be managed empirically based on personal or physician biases. Given the multitude of adjuvant therapeutic regimens that have been tested in different RCTs with somewhat similar survival outcomes, it has become increasingly difficult to select one regimen as the contemporary standard of care in this cohort. The findings of this report can help guide therapeutic decision-making in this vulnerable population suffering from an incurable disease with limited life-expectancy. The present NMA compares various adjuvant therapy regimens in elderly GBM with each other using both direct and indirect comparisons to find the most optimal regimen. It establishes and confirms that moderately hypofractionated RT (3-weeks) with concurrent and adjuvant temozolomide provides maximum survival benefit compared to other regimens in elderly patients with newly-diagnosed GBM. It also confirms that any adjuvant therapy is better than no post-operative treatment as best supportive care alone was associated with the worst survival outcomes.

Table 2 Survival outcomes of individual randomized controlled trials of elderly patients with newly-diagnosed glioblastoma in the network meta-analysis

Study-year (ref)	Treatment arms	Number of pts (N)	Follow-up (month)	Median PFS (month)	HR (95% CI) P value	Median OS (mth)	HR (95% CI) p-value	OS at 1 year (%)
Roa 2004 [15]	Normofractionated RT (6-wk)	47	NA	NA	NA	5.1 mth	0.89 (0.6–1.35) p = 0.57	44.7*
	Hypofractionated RT (3-wk)	48		NA		5.6 mth		41.7*
Guibert 2007 [16]	Normofractionated RT (5.5-wk)	39	4.9	**3.8**	**0.28 (0.17–0.47) p < 0.001**	**6.8**	**0.47 (0.29–0.76) p = 0.002**	**12**
	Best supportive care alone	42		**1.3**		**3.9**		**0**
Malmstrom 2012 [17]	TMZ monotherapy	119	NA	NA	NA	**8.3**	**0.70 (0.52–0.93) p = 0.01**	27
	Hypofractionated RT (2-wk)	123		NA	NA	7.5	0.85 (0.64–1.12) p = 0.24	23
	Normofractionated RT (6-wk)	100		NA	NA	**6**	**1 (reference)**	**17**
Wick 2012 [18]	TMZ monotherapy	195	25.2	**3.3**	**1·15 (0.92–1·43) p = 0·043**	**8.6**	**1.09 (0.84–1.42) p = 0.03**	34.4
	Normofractionated RT (6-wk)	178		**4.7**		**9.6**		37.4
Perry 2017 [19]	Hypofractionated RT (3-wk)	271	17	**3.9**	**0.50 (0.41–0.60) p < 0.001**	**7.6**	**0.67 (0.56–0.80) p < 0.001**	**22.2**
	Hypofractionated RT (3-wk) + TMZ	271		**5.3**		**9.3**		**37.8**
de Castro 2017 [21]	Hypofractionated RT (3-wk)	35	NA	3.2	p = 0.706	6.2	p = 0.936	10
	Extremely hypofractionated RT (1-wk)	26		4.3		6.8		18
Wirsching 2018 [22]	Hypofractionated RT (3-wk) + BEV	50	NA	**7.6**	**0.36 (0.20–0.65) p = 0.003**	12.1	1.09 (0.63–1.89) p = 0.77	54
	Hypofractionated RT (3-wk)	25		**4.8**		12.2		56

Statistically significant results are highlighted in bold

Pts patients, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *wk* weeks, *RT* radiotherapy, *TMZ* temozolomide, *BEV* bevacizumab, *NA* not available

*OS reported at 6-months and not at 1-year

The non-inferiority of moderately hypofractionated RT (2–3 weeks) for survival compared to normofractionated RT (6-weeks) in elderly GBM was established by two RCTs [15, 17] with the added benefit of reduced overall treatment time, number of hospital visits, and resultant resource-sparing and cost-saving. More recently, the addition of temozolomide (concurrent and adjuvant) to moderately hypofractionated RT further improved survival compared to moderately hypofractionated RT alone with modest and acceptable increase in toxicity [19]. Unfortunately, in the elderly cohort, not a

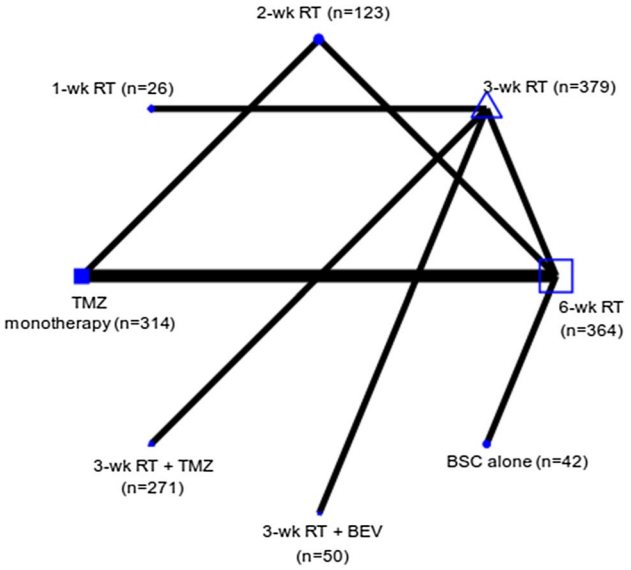

Fig. 2 Network geometry of randomized controlled trials comparing various adjuvant therapy regimens in elderly patients with newly-diagnosed glioblastoma. Each regimen is depicted as a node (number of patients in parentheses) with solid lines representing direct comparisons between any two interventions in the network

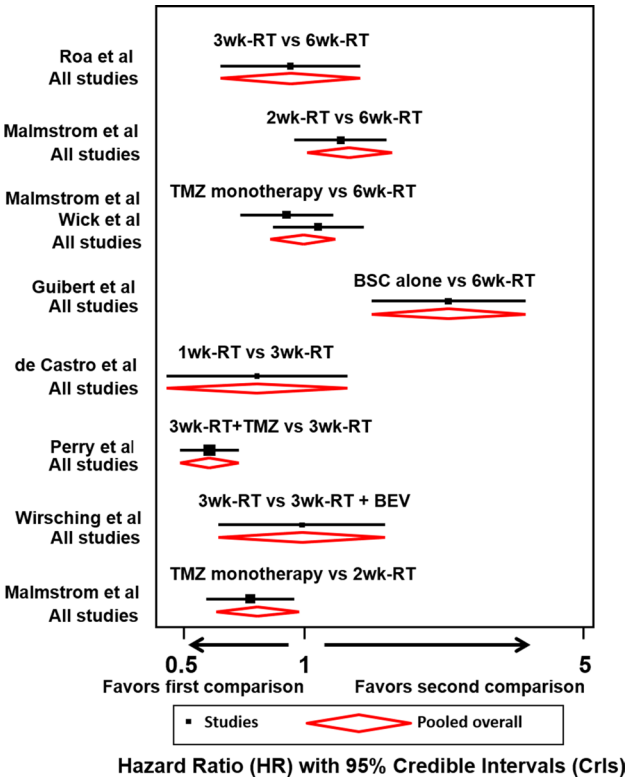

Fig. 3 Pair-wise comparison of different interventions for overall survival in elderly patients with newly-diagnosed glioblastoma. Point estimates of the hazard ratio (HR) with 95% credible intervals (CrIs) for individual studies are represented as solid black line, while the red diamond denotes the pooled estimate of that comparison across all studies

single RCT has directly compared moderately hypofractionated RT (2–3 weeks) plus temozolomide (best therapeutic option in elderly GBM) versus normofractionated RT plus temozolomide (current standard of care in non-elderly GBM) precluding any definitive or robust conclusions. However, propensity-matched analyses in two separate elderly cohorts [26, 27] have demonstrated no significant difference in survival between the two approaches, thereby suggesting non-inferiority of hypofractionated RT combined with temozolomide. A National Cancer Database study [28] evaluating practice patterns, outcomes, and predictors of survival in elderly glioblastoma patients aged 65 years and above, treated with definitive adjuvant chemoradiotherapy, reported increasing use of hypofractionated chemoradiotherapy over time. The authors also reported significant negative selection bias with patients undergoing hypofractionated chemoradiotherapy being older, with worse performance status, and undergone biopsy only. Normofractionated chemoradiotherapy was associated with improved median survival compared to hypofractionated chemoradiotherapy (10.7 vs. 6.2 months; $p < 0.001$), which persisted both on Cox multivariate analysis yielding a hazard ratio (HR) of 0.59 with 95% confidence interval (CI) ranging from 0.49 to 0.72 ($p < 0.001$) and propensity-matched analysis (median OS 8.7 vs. 6.2 months; HR = 0.69; 95% CI 0.53 to 0.89; $p = 0.005$). More recently, a meta-analysis [29] of 917 patients from seven non-randomized studies comparing hypofractionated RT plus temozolomide versus standard (normofractionated) RT plus temozolomide in elderly glioblastoma reported comparable PFS between the two regimens with a mean difference (MD) of 0.3 months (95% CI −2.4 to 2.9; $p = 0.85$), but significantly shorter OS (MD = − 3.5 months, 95% CI −6.3 to −0.6; $p = 0.02$) in the hypofractionated RT plus temozolomide arm, re-kindling the debate. In patients with RPA class V and VI glioblastoma (elderly, or frail, or both), temozolomide monotherapy has now been demonstrated to be associated with worse clinical outcomes (PFS, OS, and quality-adjusted survival) compared to moderately hypofractionated RT (30 Gy in 6 fractions over 2 weeks) in a small RCT that was terminated prematurely due to poor accrual [23]. A Cochrane review is currently underway to determine the most effective and best tolerated approach for the treatment of elderly patients with newly-diagnosed GBM [30] that could provide the highest level of evidence to guide therapeutic decision-making.

Prognsotic and predictive role of O^6-methylguanine-DNA-methyltransferase (MGMT)

In all the seven included RCTs, patients were not assigned treatment or stratified based on *MGMT* gene promoter methylation status. Four studies (17,18,19,22), however,

Table 3 Ranking of various adjuvant therapy regimens for overall survival in the network meta-analysis

Ranking	Adjuvant therapy regimens							
	6-wk RT	3-wk RT	2-wk RT	1-wk RT	3-wk RT + TMZ	3-wk RT + BEV	TMZ monotherapy	BSC alone
1st (best)	0.0	0.0	0.0	16.7	**81.0**	1.9	0.4	0.0
2nd best	4.2	4.0	0.1	49.6	18.1	17.2	6.8	0.0
3rd best	13.5	29.1	0.4	14.1	0.8	25.7	16.4	0.0
4th best	21.6	32.8	1.9	7.9	0.1	16.4	19.4	0.0
5th best	35.9	17.0	4.9	4.4	0.0	9.3	28.4	0.0
6th best	24.0	13.2	14.1	4.7	0.0	16.0	27.8	0.2
7th best	0.7	3.9	77.5	2.5	0.0	12.7	0.7	2.0
8th best (worst)	0.0	0.0	1.2	0.1	0.0	0.9	0.0	**97.8**
Mean rank	4.6	4.2	6.7	2.6	1.2	4.2	4.6	8.0
SUCRA	0.5	0.5	0.2	0.8	1.0	0.5	0.5	0.0

All numbers are expressed as percentages. Treatment with best rank (3-wk RT + TMZ) and worst rank (BSC alone) are highlighted in bold. SUCRA of 0.8 for 3-wk RT + TMZ and 0.0 for BSC alone

Wk week, *TMZ* temozolomide, *BEV* bevacizumab, *BSC* best supportive care, *SUCRA* surface under the cumulative ranking

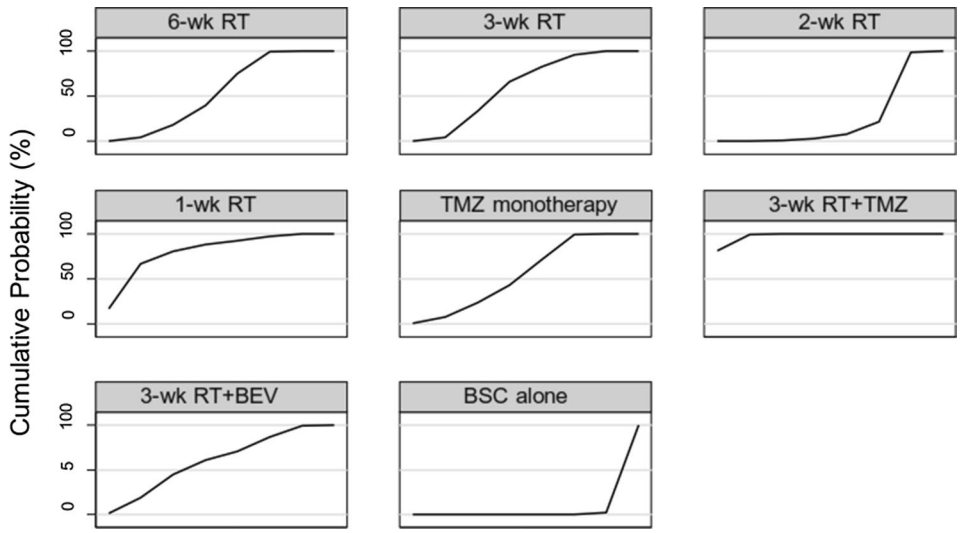

Fig. 4 Graphical ranking of adjuvant therapy regimens for overall survival in elderly patients with newly-diagnosed glioblastoma using surface under the cumulative ranking (SUCRA) curve. SUCRA is a numeric presentation of the overall ranking and presents a single number associated with each treatment with values ranging from 0 to 100%. The higher the SUCRA value of any particular intervention, and the closer to 100%, higher the likelihood that the particular intervention represents the best treatment option; lower and closer the SUCRA value to 0 for any particular intervention, more likely that the particular intervention represents the worst treatment option

did report outcomes of subset analysis based on availability of methylation status in variable proportions of patients. As expected, patients with methylated *MGMT* gene promoter had significantly better overall survival compared to patients with unmethylated tumors in each of these 4 studies, irrespective of treatment, re-inforcing the strong and independent prognostic impact of *MGMT* methylation status on outcomes in elderly GBM. The potential use of *MGMT* methylation as a predictive marker for selecting elderly patients for adjuvant chemotherapy with temozolomide was suggested by two European studies (17,18), that demonstrated superior outcomes with temozolomide monotherapy compared to RT alone in patients with methylated *MGMT* with the converse being true for unmethylated patients. However, even in patients with unmethylated tumors, the addition of temozolomide chemotherapy concurrently during RT and subsequently as adjuvant leads to a clinically meaningful improvement in survival (19), precluding the use of *MGMT* methylation status alone as an independent factor in selecting patients for combined modality treatment.

Caveats and limitations

Despite inherent advantages of NMA that combines direct and indirect comparisons, certain caveats and limitations remain. Synthesis of data and meta-analyses was limited to survival outcomes without pooling the data for toxicity or QOL, as they were not reported uniformly across all studies precluding quantitative synthesis. Given the limited life-expectancy in elderly GBM, toxicity and QOL are also important endpoints which could guide therapeutic decision-making. Apart from age, other covariates such as performance status, extent of resection, and *MGMT* methylation are known prognostic factors that can impact upon outcomes, but, were not accounted for in the analysis. However, randomization would have ensured that baseline characteristics were well-balanced in the primary studies, eliminating selection bias. Finally, this analysis was based on summary statistics extracted from published reports rather than pooling of individual patient data.

Conclusions

This is the first attempt to rank various adjuvant therapy options in the management of elderly patients with newly-diagnosed GBM using a network of prospective randomized trials. Moderately hypofractionated RT (3-weeks) with concurrent and adjuvant temozolomide emerged as the best treatment option and should be considered the most optimal and preferred adjuvant therapeutic regimen in this cohort.

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Compliance with ethical standards

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

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