# Determining the Optimal Adjuvant Therapy for Improving Survival in Elderly Patients with Glioblastoma: A Systematic Review and Network Meta-analysis

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## ABSTRACT

**Purpose:** Older patients with glioblastoma (GBM) are underrepresented in clinical trials. Several abbreviated and standard chemoradiotherapy regimens are advocated with no consensus on the optimal approach. Our objective was to quantitatively evaluate which of these regimens would provide the most favorable survival outcomes in older patients with GBM using a network meta-analysis.

**Experimental Design:** MEDLINE, Embase, Google Scholar, and the Cochrane Library were searched. Patients >60 years of age with histologically confirmed GBM were included. Primary outcome of interest was the pooled HR from randomized controlled trials (RCTs). Secondary outcomes of interest included pooled HR from studies controlling for MGMT promoter methylation status, and safety.

**Results:** Fourteen studies, including 5 RCTs, reporting 4,561 patients were included. Using highest quality data from RCTs, our network-based approach demonstrated that standard radiotherapy (SRT) and temozolomide (TMZ) provided similar survival benefit when compared with hypofractionated radiotherapy (HRT) and TMZ [HR = 0.90; 95% confidence interval (CI), 0.43–1.87], TMZ alone (HR 1.25; 95% CI, 0.69–2.26), HRT alone (HR = 1.34; 95% CI, 0.73–2.45), or SRT alone (HR = 1.43; 95% CI, 0.87–2.36). HRT-TMZ had the highest probability (85%) of improving survival in older patients with GBM followed by SRT-TMZ (72%). Pooled analysis of trials controlling for *MGMT* promoter methylation status demonstrated that TMZ monotherapy confers similar survival benefit to combined chemoradiotherapy.

**Conclusions:** Statistical comparisons using a network approach demonstrates that the common treatment regimens for older patients with GBM in previous RCTs confer similar survival benefits. Adjustments for MGMT promoter methylation status demonstrated that radiotherapy alone was inferior to TMZ-based approaches. Head-to-head comparison of TMZ monotherapy to combined TMZ and radiation is warranted.

## Introduction

Glioblastoma (GBM) is the most common primary brain tumor in adults and its incidence increases with age. In population-based studies, the median age at diagnosis is 65–67 years (1), while the median age of patients included in contemporary clinical trials is only 54–57 years. This may limit the generalizability of trial results and fail to address the needs of a general GBM population. The current standard-of-care treatment protocol, commonly referred to as the "Stupp Protocol," includes maximal safe tumor resection followed by daily temozolomide (TMZ; 75 mg/m$^2$ orally) and concurrent radiotherapy (60 Gy in 30 fractions) followed by adjuvant TMZ (150–200 mg/m$^2$) for 6 months (2). This approach prolonged survival with a HR of 0.62 [95% confidence interval (CI), 0.51–0.75], translating into an increase in median survival by 2.5 months and a 2-year survival rate of 27% compared with 10% with radiation alone. However, in older patients, 60–70 years of age, that survival advantage was less pronounced [HR = 0.70; 95% CI, 0.5–0.97) and this landmark study excluded patients older than 70 years.

On the basis of concerns for increased treatment-associated toxicity in often multimorbid older patients as well as the 6-week duration for daily radiotherapy, alternative abbreviated treatment regimens including hypofractionated radiotherapy (higher dose per fraction but less treatment fractions) and radiation-free chemotherapy-only regimens have been proposed for older patients with GBM (3, 4). However, there is little consensus on the optimal adjuvant therapy for older and/or more frail patients with GBM. Moreover, although MGMT promoter methylation has been found to be a prognostic and predictive biomarker for treatment response, its role and relevance in older patients has not been clearly demonstrated. To address these uncertainties, we performed a systematic review and network meta-analysis comparing the efficacy of differential radiation regimens with and without concurrent TMZ or TMZ alone in older patients with GBM. Use of a network meta-analysis was ideal for this scenario in which multiple different treatment regimens were compared using both direct head-to-head comparisons of interventions within various trials as well as indirect comparisons across different trials based on a common comparator. The World Health Organization has recently used network meta-analyses to create practice guidelines for management of HIV and hepatitis C virus (HCV; ref. 5). Because of its versatility compared with traditional meta-analyses, which relies on traditional direct pairwise comparisons and the increasing quantity and heterogeneity of available trials, it has been suggested that network meta-analyses should be regarded as the highest level of evidence when developing treatment guidelines (6–8).

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## Translational Relevance

Currently, there is no consensus on the optimal adjuvant treatment of older patients with glioblastoma. Our quantitative network-based meta-analysis demonstrates that abbreviated and standard chemoradiotherapy regimens that include temozolomide alone provide similar survival benefits and may be used in a rational manner interchangeably in instances where patients may not tolerate or warrant an extended treatment duration. Our analysis also provides rationale for the design of future randomized trials, for example, comparing exclusive temozolomide chemotherapy with combined modality temozolomide + radiotherapy in patients with *MGMT* promoter–hypermethylated tumors.

## Materials and Methods

For comparative efficacy analysis, we utilized a network meta-analysis, an extension of the classic pairwise meta-analysis, to compare multiple different treatments across trials on a common comparator in a single unified analysis. This approach synthesizes metrics of both direct and indirect comparisons to refine and generate estimates of all possible pairwise comparisons within a network (6, 9, 10). We compiled trials utilizing the following first-line treatments independently and in combination with one another: temozolomide (TMZ), standard fractionated radiotherapy (SRT), and hypofractionated radiotherapy (HRT), as these are the most commonly utilized and standardized treatment regimens for elderly patients with GBM. Estimates of treatment effect via direct comparisons were made between treatment groups within a single trial [e.g., TMZ + HRT vs. HRT in one trial; SRT vs. HRT in another trial] and an indirect comparison of treatment effect between different trials with a common comparator (HRT alone in this example) was obtained by subtracting the two direct treatment effect estimates. Multiple indirect comparisons can then be made for each treatment modality by combining the direct estimates of each path in the network. When both direct and indirect evidence of a comparison between treatment modalities is available, the treatment effect may be synthesized together to yield a network treatment effect. A single combined ranking of treatments may then be produced with probabilities of each treatment being the most effective or least effective detailed.

We conducted our systematic review and network meta-analysis based on a predefined protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension statement for reporting on network meta-analyses (11, 12).

### Search strategy

Three independent reviewers (F. Nassiri, J.Z. Wang, and J.H. Badhiwala) searched, without language restriction, MEDLINE (PubMed and Ovid), Embase, Google Scholar, and the Cochrane database through December 1, 2017. They used, in relevant combinations, keywords and MeSH (Medical Subject Heading) terms pertaining to the patient population (e.g., older, elderly), disease (high-grade glioma, glioblastoma, gliosarcoma), and therapy (e.g., chemotherapy, temozolomide, radiation, and hypofractionated). References of relevant articles were individually screened to identify additional sources for evaluation for inclusion.

### Selection criteria and data extraction

Three independent reviewers (F. Nassiri, J.Z. Wang, and J.H. Badhiwala) evaluated the studies for inclusion eligibility. Disagreements were resolved by consensus. Eligible studies included randomized and nonrandomized trials reporting on survival with TMZ, radiotherapy, or chemoradiation treatment for patients with glioblastoma aged 60 years of age or older. The 60-year age cutoff was selected on the basis of previous studies that have demonstrated an objective difference in treatment response and survival for patients within this age group compared with younger patients, and to ensure granular statistical comparisons based on how patients were stratified in previous RCTs (refs. 2, 3, 13–17). For example, in the landmark EORTC/NCIC trial by Stupp and colleagues, patients were analyzed in age subgroups <50, 50–60, and >60 with the observed treatment effect being noticeably less pronounced in patients >60 years of age (14). The Nordic trial was specifically designed for patients older than 60 years of age (3). The CCTG/EORTC trial included patients older than 65 years of age (18), and a prior Canadian trial on HRT set the cutoff at age > 60 years (19). The German NOA-08 study included comparing exclusive radiotherapy with single agent TMZ chemotherapy restricted inclusion to patients > 65 years. Single-arm studies, reports in abstract form only, conference abstracts, and studies that did not provide sufficient data to extract adjusted Hazard Ratios (HR) for death were excluded from our analysis.

Three investigators (FN, JW, JHB) independently extracted the following data from all included studies where available: study details (year of publication, country or region of enrollment, recruitment period), participant details (inclusion criteria, exclusion criteria, median age, extent of resection, MGMT methylation status), intervention (treatment arm, number of patients in each treatment arm), outcome [median progression-free survival (PFS) or overall survival (OS), HR for death, adjusted HR for death], adverse events (hematological and nonhematological), and cognitive outcomes.

Treatment regimens were categorized into the following groups for comparisons: SRT alone (typically 58–62 Gy in 30–33 fractions), HRT (defined as any total radiation dose less than the standard, typically 40 Gy/15 fractions, 34 Gy/10 fractions, or 30 Gy/5 fractions), SRT with concurrent TMZ (SRT-TMZ), HRT with concurrent TMZ (HRT-TMZ), and TMZ alone. SRT-TMZ or the "Stupp protocol" was considered the common reference treatment.

### Quality assessment

Two reviewers (FN and JW) independently performed quality assessment of the included studies using the Newcastle-Ottawa Scale (10) for nonrandomized trials and the Cochrane's Risk of Bias Tool for randomized trials (11). Disagreements were resolved by discussion and consensus with a third reviewer (JHB). In brief, these previously validated tools (Newcastle-Ottawa Scale and Cochrane) are designed to assess the quality of and risks of bias in nonrandomized and randomized studies, respectively (20–22).

### Data synthesis and statistical analysis

Our primary outcome of interest was the pooled survival hazard ratio from RCTs. Secondary outcomes of interest included outcomes of efficacy (pooled adjusted HR for non-randomized trials and for all trials controlling for MGMT promoter methylation status, a robust biomarker of response to TMZ), and safety (major

adverse events, cognition). Adjusted HR were used to pool metrics in nonrandomized trials in an attempt to control for trial-dependent factors. Factors that contributed to adjustment of the HRs were noted for each trial. RCTs were included in the analysis controlling for MGMT methylation status given that randomization would theoretically limit bias for MGMT promoter methylation status in either treatment arm.

For both our primary and secondary outcomes, we generated a network-node plot of comparisons to illustrate the number of trials that formed direct comparisons between treatment groups. We conducted a standard random effects model meta-analysis of pairwise direct comparisons between interventions, as well as a network meta-analysis exploiting both direct and indirect comparisons using a frequentist network meta-analysis. SRT-TMZ was used as the reference treatment for indirect comparisons. Estimates of the relative effects of all pair-wise comparisons were reported as HR for death with 95% CI in a league table. *P*-scores were computed and used to rank each treatment as the best treatment strategy. Local consistency, a measure of agreement between direct and indirect comparisons, was assessed by comparing estimates produced by direct with indirect comparisons, and overall network consistency was assessed by computing the Q statistic (23, 24). Heterogeneity, a measure of similarity in reported outcomes in the network, was assessed with the Cochrane's Q test and reported with the $I^2$ statistic within each pairwise comparison, with $I^2$ values exceeding 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively (25). An alpha error of <0.05 was considered as statistically significant. All analyses and data manipulation were performed in R version 3.4.0 (http://www.R-project.org/)

# Results

## Characteristics of included studies

Our literature search yielded a total of 1995 results. We excluded 1926 articles after removal of duplicates and title and abstract screen. We performed full-text reviews of 69 articles. A total of 14 articles (5 RCTs and 9 non-RCTs) met our aforementioned criteria and were included in our network meta-analysis (**Fig. 1**; refs. 3, 4, 13, 14, 18, 19, 26–35). Study characteristics of the randomized and nonrandomized studies included in our analysis are summarized in **Tables 1** and **2**. Data were extracted from the published literature.

## Quality of evidence

The overall risk of bias in all 5 randomized trials was low based on the Cochrane Collaboration tool for assessing risk of bias. Seven of the 9 nonrandomized studies were deemed to be of high quality (≥7/9 points on the Newcastle-Ottawa scale). Detailed quality assessments of both randomized and nonrandomized studies included in our analysis can be found in Supplementary Tables S2 and S3, respectively.

## Survival

For the primary outcome, five RCTs comparing 5 unique treatment regimens with 7 direct comparisons were pooled in our network meta-analysis (**Fig. 2**) with moderate degree of heterogeneity ($I^2 = 60.6\%$, $P = 0.079$). When comparing single modality therapies (either radiotherapy or chemotherapy alone), there was no significant difference in survival when comparing HRT alone to SRT alone (HR = 0.94; 95% CI, 0.67–1.31) or TMZ alone (HR = 1.07; 95% CI, 0.73–1.58; **Table 3**). When combined therapies were introduced into the comparison, there

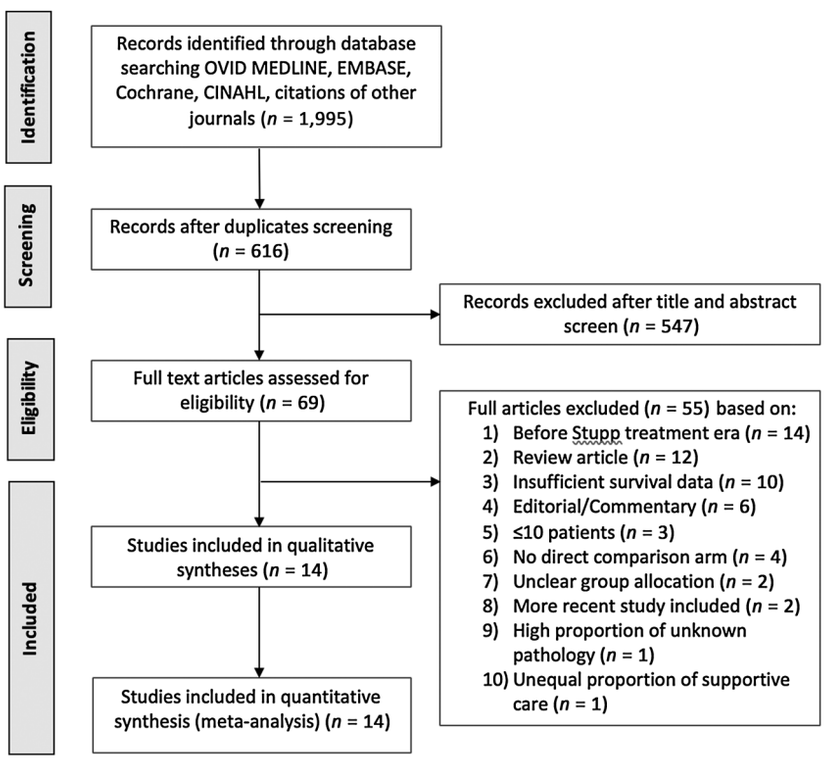


**Figure 1.**
PRISMA flow diagram of Medline search.

**Table 1.** Characteristics of included studies.

| | Study | Minimum age | Study duration | Treatment arms | No. of patients | Median age | Median KPS (range) | Factors controlled in multivariate analysis |
|---|---|---|---|---|---|---|---|---|
| Randomized trials | Malmstrom et al. (2012) | 60 | 2000–2009 | TMZ | 93 | 70 (60–88) | | Age, extent of resection, WHO performance score |
| | | | | HRT | 98 | 70 (60–83) | | |
| | | | | SRT | 100 | 70 (60–80) | | |
| | Perry et al. (2017) | 65 | 2007–2013 | HRT | 281 | | | Age, ECOG, extent of resection, MMSE score, MGMT |
| | | | | HRT, TMZ | 281 | | | |
| | Roa et al. (2004) | 60 | 1996–2001 | SRT | 47 | 72.4 (mean) | 70 (IQR, 60–80) | N/A |
| | | | | HRT | 48 | 71.0 (mean) | 70 (IQR, 60–80) | |
| | Stupp et al. (2009) | 60 (subgroup) | 2000–2002 | SRT | 278 | | | N/A |
| | | | | SRT, TMZ | 254 | | | |
| | Wick et al. (2012) | 65 | 2005–2009 | TMZ | 195 | 72 (66–84) | 80 (60–100) | Age, histology, extent of resection, MGMT, treatment group |
| | | | | SRT | 178 | 71 (66–82) | 80 (60–100) | |
| Nonrandomized trials | Chang-Halpenny et al. (2015) | 65 | 2003–2012 | SRT, TMZ | 100 | 69 (65–93) | 90 (50–100) | Age, KPS, RPA, RT dose, extent of resection, BV, tumor focality, MGMT |
| | | | | HRT, TMZ | 29 | 75 (66–87) | 70 (30–90) | |
| | Wang et al. (2016) | 60 | 1994–2014 | SRT, TMZ | 157 | 66 | ≥70 | Age, KPS, RPA, RT dose, extent of resection, RT planning |
| | | | | HRT, TMZ | 25 | 72 | ≥70 | |
| | Arvold et al. (2015) | 65 | 1994–2013 | HRT | 9 | 79 | 50 | Age, KPS, tumor focality, extent of resection, treatment group |
| | | | | HRT, TMZ | 34 | 78 | 70 | |
| | | | | SRT | 35 | 70 | 80 | |
| | | | | SRT, TMZ | 57 | 68 | 80 | |
| | Lombardi et al. (2015) | 65 | 2007–2014 | HRT, TMZ | 71 | Total cohort: 71 (65–84) | | ECOG, extent of resection, RT dose, MGMT, IDH1 |
| | | | | SRT, TMZ | 166 | | | |
| | Arvold et al. (2017) | 65 | 1995–2009 | SRT, TMZ | 705 | 70–74 | | Age, sex, marital status, race, median income, Deyo, tumor location/size, surveillance, epidemiology, SEER region, discharge location, extent of resection |
| | | | | SRT | 714 | 70–74 | | |
| | | | | SRT | 233 | 70–74 | | |
| | Cao et al. (2012) | 60 | 2000–2009 | HRT, TMZ | 57 | Mean 70 (60–86) | 80 (30–100) | Treatment group, extent of surgery |
| | | | | HRT | 55 | Mean 70 (60–81) | 70 (30–90) | |
| | Niyazi et al. (2012) | 70 | 2002–2009 | SRT, TMZ | 18 | 76 | 80 | Sex, KPS, TMZ |
| | | | | SRT | 25 | 75 | 80 | |
| | Behm et al. (2013) | 65 (subgroup) | 1998–2010 | SRT | 59 | 72.4 (65.8–84.8) | 60 (30–90) | Age, KPS, treatment group, extent of resection |
| | | | | SRT, TMZ | 80 | 71.6 (65.1–82.4) | 70 (50–100) | |
| | Brandes et al. (2003) | 65 | 1993–2000 | SRT | 24 | 70 (65–77) | 72.5 (60–90) | Age, KPS, residual disease, comorbidity |
| | | | | SRT, PCV | 32 | 69 (65–74) | 80 (60–90) | |
| | | | | SRT, TMZ | 23 | 68 (65–75) | 77 (60–90) | |

Note: Six cycles of adjuvant oral TMZ at dose of 150–200 mg/m$^2$ for 5 days every 28 days. HR based on subgroup analysis.

Abbreviations: BV, bevacizumab; Fr, fractions; Gr, gray; GTR, gross total resection; HRT, hypofractionated or abbreviated radiotherapy (30–40 Gy/10–15 Fr); KPS, Karnofsky performance score; OS, overall survival; PCV, procarbazine, lomustine, vincristine; RPA, recursive partitioning analysis; SEER, Surveillance, Epidemiology, and End Results Medicare Data; SRT, standard radiotherapy (59.4 Gy–60 Gy/30–33 Fr); Stupp protocol, concomitant chemotherapy consisting of oral TMZ at daily dose of 75 mg/m$^2$ given 7 days per week from first to last day of radiotherapy for a maximum of 49 days.

**Table 2.** Survival data from included studies.

| | Study | Treatment arms | No. of patients | Median age | Median OS (mo.) | 12-month survival (%) | 24-month survival (%) |
|---|---|---|---|---|---|---|---|
| Randomized trials | Malmstrom et al. (2012) | TMZ | 93 | 70 (60–88) | 8.3 (95% CI, 7.1–9.5) | 26.8 | 6.4 |
| | | HRT | 98 | 70 (60–83) | 7.5 (95% CI, 6.5–8.6) | 21.4 | 2.0 |
| | | SRT | 100 | 70 (60–80) | 6.0 (95% CI, 5.1–6.8) | 17.0 | 3.0 |
| | Perry et al. (2017) | HRT | 281 | | 7.6 (95% CI, 7.0–8.4) | 35.6[b] | 1.8[c] |
| | | HRT, TMZ | 281 | | 9.3 (95% CI, 8.3–10.3) | 45.9[b] | 8.2[c] |
| | Roa et al. (2004) | SRT | 47 | 72.4 (mean) | 5.9 (95% CI, 0.60–1.35) | 8.5 | 0 |
| | | HRT | 48 | 71.0 (mean) | 6.1 (95% CI, 0.60–1.35) | 14.5 | 0 |
| | Stupp et al. (2009) | SRT | 278 | | 2.3 (95% CI, 0.4–7.3) | 51.7 | 11.1 |
| | | SRT, TMZ | 254 | | 8.8 (95% CI, 3.6–16.9) | 68.9 | 29.9 |
| | Wick et al. (2012) | TMZ | 195 | 72 (66–84) | 8.6 (95% CI, 7.3–10.2) | 30.9 | |
| | | SRT | 178 | 71 (66–82) | 9.6 (95% CI, 8.2–10.8) | 33.1 | |
| Nonrandomized trials | Chang-Halpenny et al. (2015) | SRT, TMZ | 100 | 69 (65–93) | 13.0 (range, 2–72) | 54 | 17 |
| | | HRT, TMZ | 29 | 75 (66–87) | 5.4 (range, 1.7–30) | 8 | 1 |
| | Wang et al. (2016) | SRT, TMZ | 157 | 66 | 14.3 | 35.0[d] | 13.4[e] |
| | | HRT, TMZ | 25 | 72 | 15.8 | 12.0[d] | 0 |
| | Arvold et al. (2015) | HRT | 9 | 79 | 4.1 (range, 1.8–12.8) | | |
| | | HRT, TMZ | 34 | 78 | 9.6 (range, 2.7–75.8) | | |
| | | SRT | 35 | 70 | 9.5 (range, 2.5–41.7) | | |
| | | SRT, TMZ | 57 | 68 | 11.1 (range, 3.4–45.3) | | |
| | Lombardi et al. (2015) | HRT, TMZ | 71 | 71 (65–84) | 13.8 (95% CI, 11.7–17.9) | 61.6[a] | 24.1 |
| | | SRT, TMZ | 166 | | 19.4 (95% CI, 16.3–21.5) | 77.0[a] | 36.1 |
| | Arvold et al. (2017) | SRT, TMZ | 705 | 70–74 | 7.4 (IQR, 3.3–14.7) | 31.2 | 10.0 |
| | | SRT | 714 | 70–74 | 5.9 (IQR, 2.6–12.1) | 25.4 | 7.1 |
| | | SRT | 233 | 70–74 | 5.6 (IQR, 2.7–9.6) | 14.1 | |
| | Cao et al. (2012) | HRT, TMZ | 57 | Mean 70 (60–86) | 6.9 (95% CI, 4.5–8.6) | 23.0[a] | |
| | | HRT | 55 | Mean 70 (60–81) | 9.3 (95% CI, 5.9–11.8) | 34.7[a] | |
| | Niyazi et al. (2012) | SRT, TMZ | 18 | 76 | 6.4 (95% CI, 3.6–9.2) | 29.7[a] | 0 |
| | | SRT | 25 | 75 | 9.3 (95% CI, 5.6–13.0) | 35.5[a] | 15.2 |
| | Behm et al. (2013) | SRT | 59 | 72.4 (65.8–84.8) | 3.6 (95% CI, 3.2–4.7) | 6.7[a] | 0 |
| | | SRT, TMZ | 80 | 71.6 (65.1–82.4) | 8.7 (95% CI, 6.3–11.8) | 35.3[a] | 3.1 |
| | Brandes et al. (2003) | SRT | 24 | 70 (65–77) | 11.2 (95% CI, 9.43–13.35) | 31.7[a] | 4.6[a] |
| | | SRT, PCV | 32 | 69 (65–74) | 12.7 (95% CI, 11.2–18.74) | 55.2[a] | 6.6[a] |
| | | SRT, TMZ | 23 | 68 (65–75) | 14.9 (95% CI, 13.37–24.35) | 72.7[a] | 20.2[a] |

Abbreviations: HRT, hypofractionated or abbreviated radiotherapy (30–40 Gy/10–15 Fr); OS, median survival; SRT, standard radiotherapy (59.4 Gy–60 Gy/30–33).
[a]Digitized estimate based on data from Kaplan–Meier survival curve.
[b]10-Month survival.
[c]25-Month survival.
[d]500-Day survival.
[e]750-Day survival.

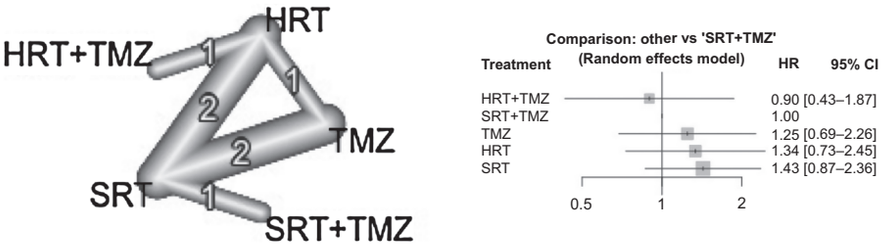


**Figure 2.**
Results from network meta-analysis for primary outcome pooling HR for death from RCTs. Left, network node plot. Each node represents a treatment regimen and interconnecting lines represent direct comparisons within the network. Right, results of network meta-analysis demonstrated in forest plot with SRT + TMZ as reference treatment. All studied treatment regimens provide similar survival benefit.

was a trend toward improved survival with HRT + TMZ compared with any of the monotherapy groups, be it HRT alone (HR = 0.67; 95% CI, 0.44–1.01), SRT alone (HR = 0.63; 95% CI, 0.37–1.07) or TMZ alone (HR = 0.72; 95% CI, 0.41–1.72). A similar trend was seen with SRT + TMZ when compared with HRT alone (HR = 0.74; 95% CI, 0.40–1.36), SRT alone (HR = 0.70; 95% CI, 0.42–1.15), or TMZ alone (HR = 0.81; 95% CI, 0.44–1.47). The probability ranking of all these treatment regimens demonstrated that HRT + TMZ had the highest probability of being the best overall treatment, followed by SRT + TMZ (**Fig. 3**). There was no statistical evidence of inconsistency in the network meaning that direct and indirect comparisons were largely congruent ($Q = 5.12$, $P = 0.077$; Supplementary Table S4). The relative effect measures for all possible treatment comparisons from the network meta-analysis are demonstrated in **Table 3** and results are graphically displayed in comparison with the reference treatment (SRT-TMZ) in **Fig. 2**.

For the secondary efficacy outcome, 9 retrospective, nonrandomized studies comparing 5 unique treatment regimens with 14 direct comparisons were pooled (**Fig. 4A**). The relative effect measures for all possible treatment comparisons from the network meta-analysis of all nonrandomized trials are demonstrated in Supplementary Table S5 and results are graphically displayed in comparison with the reference treatment in **Fig. 4A**. Pooling of data from nonrandomized trials suggest that SRT + TMZ provides a robust and statistically significant survival benefit compared with HRT alone (HR = 0.36; 95% CI, 0.14–0.917).

We performed an additional analysis for all trials (randomized and nonrandomized) that controlled for MGMT promoter methylation status (3, 4, 18). There were 7 articles comparing 5 unique treatment regimens with 9 direct comparisons pooled in this network. The relative effect measures from the network meta-analysis of all MGMT methylation–controlled trials is graphically displayed in **Fig. 4B** and in Supplementary Table S6. Pooling of trials that controlled for MGMT methylation status either by study design or statistics demonstrated that SRT + TMZ provided a similar survival benefit as other TMZ-based approaches including TMZ monotherapy (HR = 1.56; 95% CI, 0.86–2.83) and HRT + TMZ (HR = 1.51; 95% CI, 0.82–2.76). Therapies that incorporated TMZ had improved survival compared with radiation monotherapy treatments (SRT HR = 1.82; 95% CI, 1.09–3.03; HRT HR = 1.87; 95% CI, 1.05–3.31) for MGMT-methylated patients. Probability ranking for MGMT methylation–adjusted analysis demonstrated that SRT + TMZ had the highest probability of being ranked as the best overall treatment, followed by HRT + TMZ (**Fig. 3**).

## Safety

The variable reporting of adverse events (AE) across all included studies and precluded meaningful pooled analyses. Of the three studies comparing SRT and HRT, only 1 reported on AEs in detail (3). Malmstrom and colleagues reported nonhematologic AEs in the radiotherapy groups and largely similar rates of nonhematologic AEs between the HRT and SRT groups, with higher rates of infection/fever and seizures in the SRT group (13.7% and 12.6%, respectively) compared with HRT group (6.4% and 6.4%, respectively; ref. 3). There was also 1 infection-related fatality in the SRT secondary to high-dose steroid use (3). Treatment paradigms that included concurrent TMZ resulted in higher rates of hematologic AEs, including higher rates of grade 3–4 toxicity (e.g., leukopenia, anemia, lymphopenia, neutropenia, and thrombocytopenia); however, the rate of AEs leading to death were similar (13, 14, 18). Treatment with SRT compared with TMZ resulted in more cutaneous adverse events (4). Of the five studies comparing SRT + TMZ and HRT + TMZ, only 1 reported on differential AEs between the groups. In this study, there was a similar rate of grade 3–4 hematologic toxicity in the 40 Gy group compared with the 60 Gy group (11.2% vs. 10.2%, respectively), although all patients received TMZ in each group. Of 53 patients who received reduced or delayed TMZ due to therapy toxicity, 28% were from the 40 Gy radiation group and 20% were from the 60 Gy group (35).

**Table 3.** League table representing pooled result of network meta-analysis.

| | HRT[a,b,c] | HRT/Stupp[b] | SRT[a,c,d,e] | SRT/Stupp[d] | TMZ[a,e] |
|---|---|---|---|---|---|
| HRT[a,b,c] | — | 1.49 (1.01–2.27) | 0.94 (0.67–1.31) | 1.34 (0.73–2.45) | 1.07 (0.73–1.58) |
| HRT/Stupp[b] | 0.67 (0.44–1.01) | — | 0.63 (0.37–1.07) | 0.90 (0.43–1.87) | 0.72 (0.41–1.72) |
| SRT[a,c,d,e] | 1.06 (0.76–1.49) | 1.59 (0.93–2.72) | — | 1.43 (0.87–2.36) | 1.14 (0.83–1.58) |
| SRT/Stupp[d] | 0.74 (0.40–1.36) | 1.11 (0.53–2.32) | 0.70 (0.42–1.15) | — | 0.81 (0.44–1.47) |
| TMZ[a,e] | 0.93 (0.63–1.36) | 1.39 (0.79–2.44) | 0.87 (0.63–1.20) | 1.25 (0.69–2.26) | — |

Note: Data are presented as HR (95% CI).
Abbreviation: Stupp, 60 Gy/30 Fr + concomitant and adjuvant TMZ; TMZ, temozolomide.
[a]Malmstrom and colleagues (2012).
[b]Perry and colleagues (2017).
[c]Roa and colleagues (2004).
[d]Stupp and colleagues (2009).
[e]Wick and colleagues (2012).

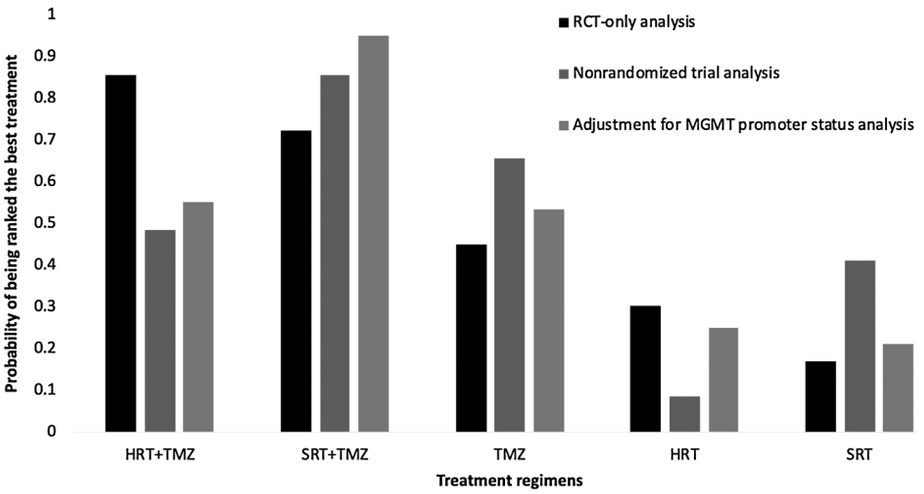


**Figure 3.**
Probability of each treatment being ranked the best treatment from pooling of randomized trials only, nonrandomized trials only, and trials controlling for MGMT promoter methylation status.

Only one study reported on changes in cognition after treatment. In this study, Mini-Mental Status Examination scores did not differ 3 months after randomization between the TMZ alone and SRT alone groups in patients greater than 65 years of age (4). Other studies that attempted to assess cognition as a component of quality of life, such as through the FACT-Br assessment, were unable to reach meaningful conclusions due to suboptimal patient reporting or compliance, poor accrual, and attrition.

## Discussion

We performed a network meta-analysis of the existing literature to determine the optimal adjuvant treatment strategy in patients with GBM over the age of 60 years. Our results suggest that all treatment regimens studied provided similar treatment benefits in older patients with GBM. After controlling for MGMT promoter methylation status, we observed that TMZ-based approaches either in combination with radiotherapy or as monotherapy provide a survival benefit for older patients with GBM compared with radiotherapy-only approaches. Abbreviated radiotherapy may also be associated with slightly less nonhematologic (primarily cutaneous) adverse effects compared with SRT. Overall, pooled analysis from RCTs only suggests that HRT/TMZ had the greatest probability of being ranked as the optimal treatment in older patients with GBM.

Our study is unique in that we performed a quantitative synthesis of results via a network meta-analysis that allowed for comprehensive comparison (both direct and indirect) of all different common

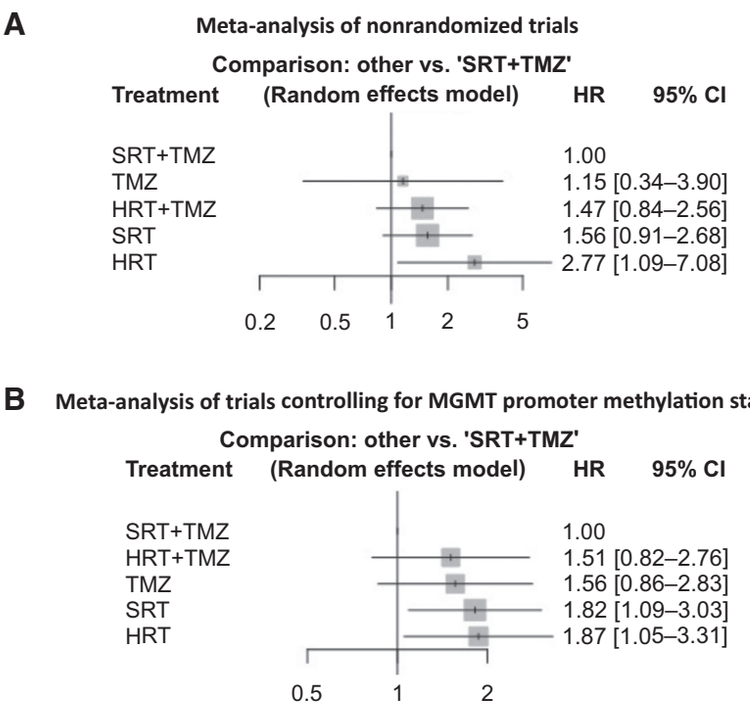


**Figure 4.**
Forest plot demonstrating results of network meta-analysis for network pooling nonrandomized trials only (**A**) and network pooling trials controlling for MGMT promoter methylation status (**B**).

treatment strategies (combined therapy and radiation or TMZ monotherapy) used in older patients. We were also able to include data from nonrandomized trials to expand our sample size and increase the power of our comparisons. Our outcome of interest was pooled HR for death in randomized trials and adjusted HR for death in nonrandomized trials, which are the most robust outcomes to pool to assess for differences in time-to-death comparisons (36). Although we were unable to perform extensive subgroup analysis due to variability in the reporting of confounders, the use of the adjusted HR as our outcome allowed for control of some confounding variables during pooled analysis. Moreover, we were specifically able to report on outcomes after controlling for MGMT promoter methylation status by pooling results from trials where MGMT-methylated tumors would have unbiased allocation to each treatment arm and from nonrandomized trials where the HRs were statistically adjusted by multivariable analysis.

Although we were unable to perform meaningful pooled analysis of adverse events due to heteroegenity in reporting, we observed that the use of TMZ was generally associated with more hematologic adverse events (including grade 3/4) and slightly higher rates of infection/fevers, but lower rates of cutaneous side effects compared to radiotherapy. SRT was associated with slightly greater nonhematologic side effects compared with HRT including seizures and infection/fever. Taken in combination with our findings that demonstrated similar survival with abbreviated chemoradiotherapy or TMZ monotherapy in comparison with standard therapy, we suggest that these are viable alternatives to more protracted treatment regimens and may spare older patients from treatment-associated toxicities.

We are not aware of any standard definition for "older" patients. Given that the results of the EORTC-NCIC trial were notably different in patients older than 60 years of age, and that previous reviews have included the age of 60 years as a cutoff to define an older population (37), we used an age cutoff of 60 for our study. It is important to note that the median age of most cohorts included was around 70 years (**Table 1**). Age stratification used in a number of previous RCTs allowed for using the age limit of greater than 60 years for granular statistical comparisons. It is important to note that there may have been a bias to inclusion of patients with negative prognostic factors in these trials while healthy and fit "older" patients were to receive the standard "Stupp regimen."

We are aware of one other systematic review on this topic (37). This study included six articles dating up to August 2013 and defined an "older" population as patients greater than 60 years of age, same as in our report. Synthesis of the results was based on narrative review without quantitative comparisons, and the authors concluded that TMZ monotherapy or HRT may be viable alternatives for older patients with GBM who are unable to tolerate the standard "Stupp protocol." However, at the time, the RCT by Perry and colleagues was not yet published and its results have provided significant insight in terms of the additive benefit of TMZ onto an already abbreviated radiotherapy regimen for elderly patients who may not tolerate SRT (18). In addition to this, pooled quantitative results controlling for MGMT-methylated promoter status were included in our analyses.

Our results should be viewed in light of the limitations of our study. First, previous trials including the Nordic trial, NOA-08, and the CCTG-EORTC have all demonstrated that patients with methylated MGMT status have improved overall survival when treated with TMZ (3, 4, 18). We were unable to perform a subgroup analysis based on MGMT promoter methylation status due to a surprisingly high number of contemporary trials lacking granular reporting of this information. However, we were able to perform a pooled secondary efficacy outcome that included trials reporting on HRs adjusted for MGMT promoter methylation status. Our finding that treatment regimens with TMZ, including TMZ monotherapy, may improve survival in patients with methylated MGMT promoter status compared with regimens that did not provides rationale for head-to-head RCT comparing TMZ monotherapy to combined chemoradiotherapy regimens in patients with MGMT promoter methylation. Second, the extent of the initial surgical resection was accounted for in most but not all of our included studies (13/14 included). However, reporting was inconsistent in regard to what defined subtotal versus a gross total resection, with some studies reporting on near total resections that did not fall into either category. Of note, in all studies, subtotal resection and/or gross total resection conferred improved survival compared with biopsy alone. Given that patients were randomized to therapies in these trials, we would expect the proportion of gross total and subtotal resected patients to be similar in different treatment arms at least within each trial. In addition, we were also unable to assess whether there were relevant differences in baseline risks for the included patient groups in the various trials as different performance scores were used and we were unable to obtain primary data from these trials. However, it is unlikely there were meaningful baseline differences as in each individual trial, there were no significant differences in the performance scores of the treatment arms, and the vast majority of included patients had performance scores denoting independence as a prerequisite for enrollment. Finally, because the goal of our analysis was to determine optimal adjuvant therapy in the way of chemotherapy and radiation, we did not include comparisons of effectiveness of new treatment options such as tumor-treating fields (35). Therefore, future studies are warranted to similarly focus on the role of these novel approaches in older patients and their efficacy.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** F. Nassiri, S. Taslimi, J.Z. Wang, J.H. Badhiwala, T. Dalcourt, N. Ijad, N. Pirouzmand, G. Zadeh
**Writing, review, and/or revision of the manuscript:** F. Nassiri, S. Taslimi, J.Z. Wang, J.H. Badhiwala, S. Almenawer, R. Stupp, G. Zadeh
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** F. Nassiri, G. Zadeh
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