Clinical Implications of Basic Neuroscience Research

Treatment of Elderly Patients With Glioblastoma
A Systematic Evidence-Based Analysis

Oren J. Zarnett, BSc; Arjun Sahgal, MD; Jessica Gosio; James Perry, MD; Mitchel S. Berger, MD; Susan Chang, MD; Sunit Das, MD, PhD

IMPORTANCE Despite improvements in survival with aggressive chemoradiation, outcomes for patients diagnosed as having glioblastoma multiforme (GBM) remain poor. Survival is further limited in elderly patients, who are often unable to tolerate multimodality therapy. The appropriate treatment approach for elderly patients (aged >65 years) with GBM remains unclear. While the literature supports the use of standard radiotherapy (60 Gy), several recent studies have suggested that treatment with temozolomide monotherapy or short-course radiotherapy may be a reasonable alternative.

OBJECTIVE To review literature reporting survival data related to treatment of elderly patients with GBM using either temozolomide alone or radiotherapy alone.

EVIDENCE REVIEW We performed a systematic review to identify articles from the temozolomide era (2005-present) that reported survival data related to treatment of elderly patients with GBM using either temozolomide alone or radiotherapy alone, with consideration of O^6-methylguanine-DNA-methyltransferase gene (*MGMT*) promoter methylation status. PubMed was searched for articles between January 1, 2005, and August 31, 2013, using the search terms *glioblastoma*, *elderly*, *temozolomide*, *radiation*, *hypofractionated*, and *survival*, and references from relevant articles were searched. Selected articles reported overall survival data associated with either temozolomide alone or radiotherapy alone in elderly patients (aged ≥60 years) with GBM; articles were excluded if they did not report survival data from radiotherapy alone or temozolomide alone, were not restricted to an elderly population, did not report original data, were not restricted to patients with primary GBM, were a subgroup analysis of a prior article, were a case report, or could not be located in entirety. Articles were interrogated as per the criteria designated by the Oxford Centre for Evidence-Based Medicine to determine the level of evidence presented, and data from level 1 and 2 studies were used for analysis. From a review of 185 articles, 23 were selected for inclusion and final analysis. From these, we identified 2 level 1 studies and 1 level 2 study that reported overall survival in elderly patients treated with temozolomide alone, and 4 level 1 studies and 2 level 2 studies that reported overall survival in elderly patients treated with radiotherapy alone.

FINDINGS This review of the literature revealed several limitations. First, there is a paucity of randomized clinical studies comparing temozolomide alone with radiotherapy alone in elderly patients with GBM. Second, there is a lack of coherence in the literature for the definition of *elderly*. Third, the treatment paradigms used are not consistent from study to study. Regardless, the available data did allow the formulation of a recommendation based on level 1 and 2 data.

CONCLUSIONS AND RELEVANCE The literature supports the use of hypofractionated radiotherapy or temozolomide monotherapy in the treatment of elderly patients with GBM. In patients with *MGMT* promoter methylation, temozolomide monotherapy may have greater benefit than radiotherapy.

JAMA Neurol. 2015;72(5):589-596. doi:10.1001/jamaneurol.2014.3739
Published online March 30, 2015.

Supplemental content at jamaneurology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sunit Das, MD, PhD, Division of Neurosurgery, St Michael's Hospital, University of Toronto, 30 Bond St, Toronto, ON M5B 1W8, Canada (sunit.das@utoronto.ca).

Section Editor: Hassan M. Fathallah-Shaykh, MD, PhD.

The introduction of temozolomide chemotherapy concurrent with radiotherapy resulted in a paradigm shift in the treatment of glioblastoma multiforme (GBM). The European Organisation for Research and Treatment of Cancer (EORTC)–National Cancer Institute of Canada Clinical Trials Group (NCIC) trial confirmed significant improvements in overall survival (OS) and effectively set the standard of care for newly diagnosed GBM to be radiotherapy of 60 Gy in 30 fractions concurrent with daily temozolomide followed by 6 months of adjuvant temozolomide; however, these data offer little direction regarding best practice for the treatment of elderly patients with GBM, as only a minority of patients enrolled in the EORTC-NCIC trial were older than 65 years and patients older than 70 years were excluded.[1] The optimal therapeutic approach in elderly patients is of major interest as approximately half of all patients with GBM are older than 65 years, the incidence of GBM in the elderly population is increasing,[2] and many elderly individuals cannot tolerate combined therapy.[3] Significant heterogeneity in the management of elderly patients with GBM has been reported in a recent analysis of patients older than 70 years with GBM,[4] as captured in the Surveillance, Epidemiology, and End Results (SEER) registry. The study concluded that 86% of patients received some form of treatment and only 46% of patients underwent both surgery and radiation. Evidence-based guidelines for management are needed.

The results of several recent studies[5,6] have suggested that treatment with temozolomide alone for elderly patients with GBM may be a reasonable alternative to radiotherapy. In particular, this option may be most relevant in elderly patients who harbor O^6-methylguanine-DNA-methyltransferase gene (*MGMT*) promoter methylation. Epigenetic silencing of *MGMT* through promoter methylation appears to enhance the cytotoxic effect of both temozolomide and combined chemoradiation.[7] To clarify our understanding of best practice in the treatment of elderly patients with GBM, we performed a systematic analysis of the level 1 and 2 evidence available regarding treatment of elderly patients with temozolomide or radiation monotherapy, with consideration of *MGMT* promoter methylation status.

Methods

Search Strategy and Selection Criteria

We performed a systematic review to identify articles from the temozolomide era (2005-present) that reported survival data related to treatment of elderly patients with GBM using either temozolomide alone or radiotherapy alone. References for this analysis were identified by searches of PubMed between January 1, 2005, and August 31, 2013, and references from relevant articles were searched. Literature searches were performed independently by 2 of us (O.J.Z. and S.D.) and the results compared. The search terms *glioblastoma*, *elderly*, *temozolomide*, *radiation*, *hypofractionated*, and *survival* were used. There were no language restrictions. Articles were chosen for full review if the abstract or title corroborated report of OS data. The selected articles were then reviewed to confirm report of OS data associated with either temozolomide alone or radiotherapy alone in elderly patients with GBM. *Elderly* was defined as aged 60 years or older. No selection restrictions were placed on the modality, treatment dose, or duration of radiotherapy or chemotherapy used. Single-arm studies lacking a control or comparative treatment group were excluded. Twenty-three articles were selected for inclusion in the final analysis (**Figure 1**).

The 23 articles were then reviewed with a biostatistician (Kevin Thorpe, MMath) to determine the level of evidence accrued, using the criteria designated by the Oxford Centre for Evidence-Based Medicine data as our guide.[8] Six level 1 and 2 studies were identified and included in the primary analysis. Seventeen level 3 and 4 studies were also identified and studied.

Data Extraction and Analysis

The articles selected for study were interrogated to identify elderly patients with GBM treated using chemotherapy alone or radiotherapy alone. The data were parsed to retrieve the following: recruitment period, inclusion criteria (age), number of patients treated, median age, median Karnofsky Performance Status score, median OS, 1-year OS, median progression-free survival, 6-month progression-free survival, and 12-month progression-free survival. Statistical analysis was performed using source data and SPSS version 22 statistical software (SPSS Inc).

Results

We identified 2 level 1 studies and 1 level 2 study that reported OS in elderly patients treated with temozolomide alone (**Table 1**). We also identified 4 level 1 studies and 2 level 2 studies that reported OS in elderly patients treated with radiotherapy alone (**Table 2**).

Randomized Trials

The NOA-08 trial[5] and the Nordic trial[6] were the only randomized trials comparing radiotherapy alone with temozolomide monotherapy for patients aged 65 years or older. The NOA-08 trial studied 373 patients with newly diagnosed GBM or anaplastic astrocytoma and a Karnofsky Performance Status score of 60 or greater. Patients were randomized to dose-dense temozolomide (100 mg/m^2, dosed 1 week on, 1 week off) or standard radiotherapy (60 Gy in 30 fractions). Tumor response or progression was defined according to the Macdonald criteria.[13] The *MGMT* promoter methylation status was assessed by polymerase chain reaction on all patients for whom adequate tissue was available (209 of 373 patients enrolled). The primary end point was OS; the study was powered to demonstrate noninferiority. Health-related quality of life was also assessed using the EORTC Quality of Life Core Questionnaire (QLQ-C30)[14] and EORTC Quality of Life Brain-Specific Questionnaire (QLQ-BN20)[15] quality-of-life questionnaires. Of 373 enrolled patients, 298 (80%) were able to complete the study. The study concluded that temozolomide alone was not inferior to radiotherapy alone. Median OS was 8.6 months in the temozolomide group vs 9.6 months in the radiotherapy group (P for noninferiority = .03). *MGMT* promoter methylation was associated with longer event-free survival in patients treated with temozolomide monotherapy than in those treated with radiotherapy (8.4 vs 4.6 months, respectively), while patients lacking *MGMT* promoter methylation had a longer event-free survival when treated with radiotherapy than when treated with temozolomide monotherapy (4.6 vs 3.3 months, respectively). The *MGMT* status was a strong predictor of event-free sur-

Figure 1. Flowchart of Workflow

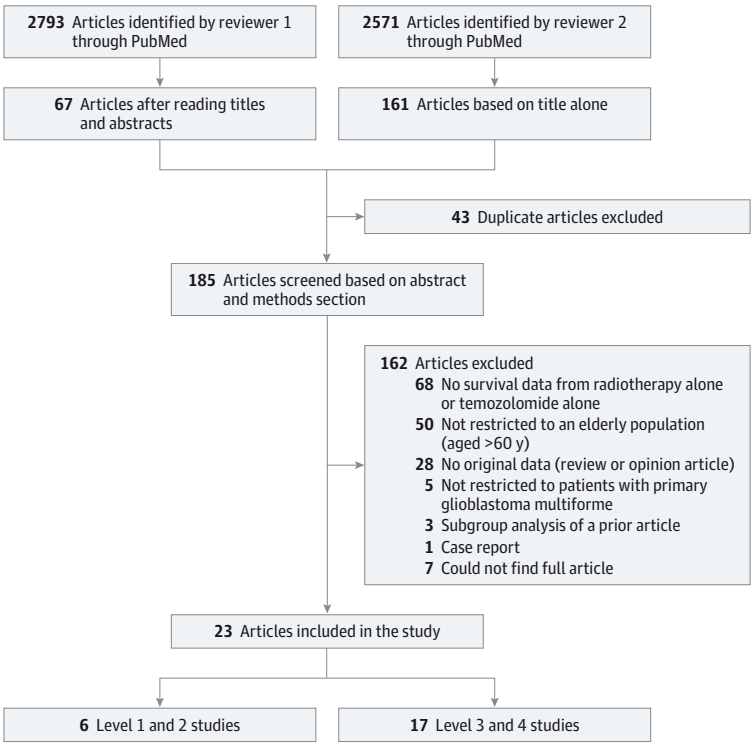


Table 1. Treatment of Glioblastoma Multiforme Using Temozolomide Alone

Source	Level of Evidence	Recruitment Period	Age, y	Patients, No.	Median (95% CI), mo	
					OS	PFS
Wick et al,[5] 2012 (NOA-08 trial)	1	2005-2009	>65	195	8.6 (7.3-10.2)	3.3 (3.2-4.1)
Malmström et al,[6] 2012 (Nordic trial)	1	2000-2009	>65	93	8.3 (7.1-9.5)	...
Reifenberger et al,[9] 2012 (German Glioma Network trial)	2	2004-2010	>70	14	8.7 (7.0-10.4)	5.0 (4.4-5.6)

Abbreviations: OS, overall survival; PFS, progression-free survival; ellipsis, not reported.

vival and showed a strong but nonsignificant effect on OS. The *MGMT*-methylated tumors responded better to temozolomide than to radiotherapy. The authors found no significant differences on quality-of-life measures among the 2 groups except for discomfort from communication deficits, which was greatest for patients in the radiotherapy group who died between 6 and 12 months of treatment.

The Nordic trial randomized 342 patients older than 65 years with a good performance status (Eastern Cooperative Oncology Group [ECOG][16] performance status score 0-2) to 3 single-modality treatment arms: (1) standard-dose temozolomide (n = 93); (2) standard radiotherapy (60 Gy in 30 fractions; n = 100); or (3) hypofractionated radiotherapy (34 Gy in 10 fractions; n = 98). Temozolomide was administered orally at 200 mg/m^2 on days 1 through 5 on a 28-day cycle for up to 6 cycles. Treatment with temozolomide was terminated prematurely on evidence of radiological or clinical progression, if unacceptable adverse effects were seen, or by physician or patient choice. After October 15, 2004, patients younger than 65 years who were deemed fit to receive combination therapy were excluded from the study. The authors unfortunately did not expand on the criteria used to determine fitness for chemoradiation. A total of 291 patients underwent treatment. The primary end point was OS; secondary end points were health-related quality of life (as measured using the EORTC QLQ-C30 and QLQ-BN20) and safety. The *MGMT* promoter methylation and *IDH1* mutation statuses were determined for all patients. Only 2 patients were found to have a tumor harboring the *IDH1* Arg132His mutation. The median OS was significantly longer in patients treated with temozolomide (8.3 months) or hypofractionated radiotherapy (7.5 months) compared with those who received standard radiotherapy (6.0 months). In patients treated with temozolomide, *MGMT* promoter methylation was associated with significantly higher survival rates than unmethylated *MGMT* promoter (9.7 vs 6.8 months, respectively) but had no effect on OS in patients treated with radiotherapy. No difference in OS was observed in patients with an unmethylated *MGMT* promoter treated with radiotherapy or single-agent temozolomide (7.0 vs 6.8 months, respectively). Patients in the temozolomide group generally reported better quality of life than

Table 2. Treatment of Glioblastoma Multiforme Using Radiotherapy Alone

Source	Level of Evidence	Recruitment Period	Age, y	Patients, No.	Median (95% CI), mo	
					OS	PFS
Wick et al,[5] 2012 (NOA-08 trial)	1	2005-2009	>65	178	9.6 (8.2-10.8)	4.7 (4.2-5.2)
Malmström et al,[6] 2012 (Nordic trial, standard radiotherapy)	1	2000-2009	>60	100	6.0 (5.1-6.8)	...
Malmström et al,[6] 2012 (Nordic trial, hypofractionated radiotherapy)	1	2000-2009	>60	100	7.5 (6.5-8.6)	...
Keime-Guibert et al,[10] 2007 (ANOCEF trial)	1	2001-2005	>70	39	7.3 (6.4-8.7)	14.9 (10.9-22.1)
Stupp et al,[11] 2009 (EORTC-NCIC trial)	1	2000-2002	>60	87	11.8 (10.4-12.7)	...
Rønning et al,[12] 2012	2	2000-2007	>70	127	7.4 (4.4-10.1)	...
Reifenberger et al,[9] 2012 (German Glioma Network trial)	2	2004-2010	>70	61	8.7 (7.0-10.4)	5.0 (4.4-5.6)

Abbreviations: ANOCEF, Association des Neuro-Oncologues d'Expression Française; EORTC, European Organisation for Research and Treatment of Cancer; NCIC, National Cancer Institute of Canada Clinical Trials Group; OS, overall survival; PFS, progression-free survival; ellipses, not reported.

did patients in the radiotherapy groups, but the ratings for global health status were equal.

In 2007, Keime-Guibert et al[10] published a randomized trial comparing supportive treatment alone with radiotherapy plus supportive care for treating patients older than 70 years with GBM (Association des Neuro-Oncologues d'Expression Française [ANOCEF] trial). Eighty-five patients with a Karnofsky Performance Status score of 70 or greater were randomized to supportive care or supportive care plus radiotherapy (50.4 Gy in 28 fractions). Prior to this study, there was no defined standard of care for the treatment of elderly patients with GBM. The study was stopped at the first interim analysis owing to the finding that OS with radiotherapy plus supportive care was superior to supportive care alone. Median OS for patients who received supportive care plus radiotherapy was 6.7 months, compared with 3.9 months in patients treated with supportive care alone. Importantly, the study found no significant difference in health-related quality of life between the 2 study groups.

The EORTC-NCIC trial compared standard radiotherapy vs chemoradiation with temozolomide in patients up to age 70 years.[11] In a subgroup analysis of 170 patients, Stupp et al[11] found that patients older than 60 years had better OS with radiation alone compared with chemoradiation (11.8 vs 10.9 months, respectively), although long-term survival was significantly greater in the chemoradiation group. However, the study was not powered to allow conclusions to be drawn regarding this elderly patient cohort. The authors did not comment on the effect of *MGMT* promoter methylation status on the efficacy of radiotherapy, but *MGMT* promoter methylation had a profound effect on OS in all patients and on progression-free survival in patients treated with chemoradiation.

Nonrandomized Trials

Reifenberger et al[9] performed a secondary analysis of 233 elderly patients with GBM (aged >70 years) identified from a prospective cohort trial (nonrandomized) enrolled in the German Glioma Network. Disease progression was defined according to the Macdonald criteria. The *MGMT* promoter methylation status was analyzed for all cases. Compared with the unmethylated *MGMT* promoter, *MGMT* promoter methylation was associated with improved OS (6.4 vs 8.4 months, respectively) and progression-free survival (4.7 vs 5.2 months, respectively). Progression-free survival was also longer in patients with *MGMT* promoter methylation treated with chemotherapy than with radiation.

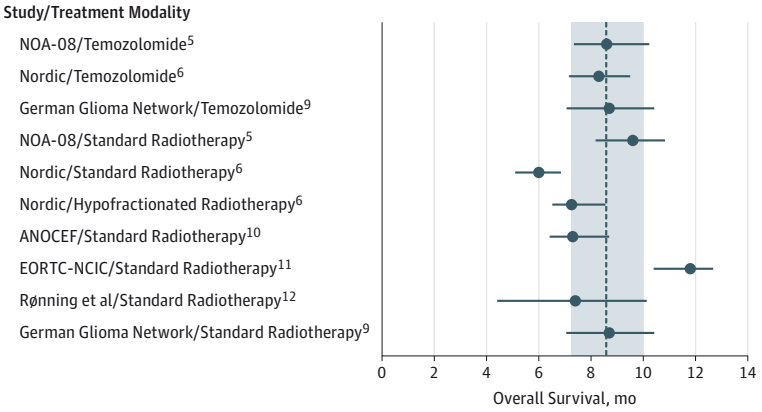
In 2012, Rønning et al[12] published a retrospective population-based analysis from a prospective, uncensored Norwegian database documenting OS in patients treated with radiotherapy alone, chemoradiation with temozolomide, or supportive care. Median OS in elderly patients (aged >70 years) treated with radiotherapy alone was 7.4 months. The addition of adjuvant chemotherapy with temozolomide conferred a significant survival advantage (median, 13.4 months; 95% CI, 10.2-19.2). The *MGMT* status was not identified.

Discussion

We performed a systematic analysis of the available level 1 and 2 evidence regarding the treatment of elderly patients with GBM treated with temozolomide or radiation monotherapy, with the goal of constructing evidence-based conclusions that can assist the clinician in decisions regarding care. Our findings suggest that chemotherapy with temozolomide is an acceptable alternative to radiotherapy in elderly patients with GBM (**Figure 2**), particularly in patients harboring *MGMT* promoter methylation (**Table 3** and **Table 4**). As shown in Figure 2, we found no significant statistical variation in effect on OS among the treatment modalities used in the reviewed trials, with the exception of a lower-than-mean OS in the standard radiotherapy group from the Nordic trial and a higher-than-mean OS in the standard radiotherapy group from the EORTC-NCIC trial. Both radiotherapy and chemotherapy are superior to supportive care alone and to historical survivals of elderly patients with GBM (median, 5.5 months) as determined through the recent SEER analysis.[17]

Our literature review is sufficient to offer level 1 evidence in support of radiotherapy for the treatment of GBM in elderly patients. The ANOCEF trial proved that radiation therapy (50.4 Gy in 28 fractions) improves OS as compared with supportive care alone, without detriment to quality of life, in patients with good performance status. Further, the Nordic trial found OS to be longer in patients treated with hypofractionated radiotherapy (34 Gy in 10 fractions) than in patients treated with standard radiotherapy (60 Gy in 30 fractions). This difference was more pronounced in older patients (aged

Figure 2. Overall Survival of Elderly Patients Treated With Temozolomide or Radiotherapy



Median overall survival with 95% CI (horizontal lines) for each treatment cohort for the NOA-08 trial,[5] the Nordic trial,[6] the German Glioma Network study,[9] the Association des Neuro-Oncologues d'Expression Française (ANOCEF) trial,[10] European Organisation for Research and Treatment of Cancer (EORTC)–National Cancer Institute of Canada Clinical Trials Group (NCIC),[11] and the study by Rønning et al.[12] Dashed line indicates mean overall survival for all patients treated; shaded area, 95% CI for mean overall survival for all patients treated.

Table 3. Effect of Treatment Modality and *MGMT* Promoter Methylation Status on OS

Source	Treatment	*MGMT* Promoter Methylation Status	Patients, No.	Median OS (95% CI), mo	HR (95% CI)	*P* Value
Wick et al,[5] 2012 (NOA-08 trial)	Temozolomide	–	77	7 (5.7-8.7)	1.34 (0.92-1.95)[a]	.13
	Temozolomide	+	31	NR (10.1-NR)	0.69 (0.35-1.16)[a]	.14
	Radiotherapy	–	59	10.4 (8.0-11.6)	1 [Reference][a]	
	Radiotherapy	+	42	9.6 (6.4-NR)	1 [Reference][a]	
Malmström et al,[6] 2012 (Nordic trial)	Temozolomide	–	44	6.8 (5.9-7.7)	1 [Reference][b]	
	Temozolomide	+	28	9.7 (8.0-11.4)	0.56 (0.34-0.93)[b]	.02
	Radiotherapy	–	68	7.0 (5.7-8.3)	1 [Reference][c]	
	Radiotherapy	+	63	8.2 (6.6-9.9)	0.97 (0.69-1.38)[c]	.81
Reifenberger et al,[9] 2012 (German Glioma Network trial)	Chemotherapy[d]	–	2	2.6 (NA)[e]	...	
	Chemotherapy[d]	+	14	7.2 (5.6-8.9)	...	
	Radiotherapy	–	30	8.8 (7.5-10.1)	...	
	Radiotherapy	+	31	7.8 (3.4-12.2)	...	

Abbreviations: HR, hazard ratio; *MGMT*, O^6-methylguanine-DNA-methyltransferase gene; NA, not applicable; NR, not reached; OS, overall survival; ellipses, not reported; –, negative, +, positive.

[a] The HR was calculated relative to radiotherapy using both tumors with *MGMT* promoter methylation and those without *MGMT* promoter methylation.

[b] The HR was determined by comparing patients treated with temozolomide who had tumors without vs with *MGMT* promoter methylation.

[c] The HR was determined by comparing patients treated with radiotherapy who had tumors without vs with *MGMT* promoter methylation.

[d] Includes 14 patients treated with temozolomide, 1 patient treated with procarbazine hydrochloride plus lomustine, and 1 patient treated with nitrosourea alone.

[e] Analysis was limited by the small sample size for this treatment (n = 2).

>70 years). The use of hypofractionated radiotherapy in elderly patients is in keeping with results published previously by Roa et al,[18] who found no OS advantage in patients older than 60 years who were treated with standard radiotherapy (60 Gy in 30 fractions) vs hypofractionated radiotherapy (40 Gy in 15 fractions). Furthermore, Roa and colleagues found benefits in using hypofractionated radiotherapy with respect to a reduction in corticosteroid dependence. While representative of a different treatment era, the data from the study by Roa and colleagues support the conclusions of the Nordic trial that hypofractionated radiotherapy is at least equivalent to standard radiotherapy in elderly patients newly diagnosed as having GBM and should be a standard-of-care treatment option offered to patients. The literature does not speak to the efficacy of radiotherapy with 60 Gy vs 50.4 Gy in the elderly population.

Both the Nordic and NOA-08 trials found temozolomide monotherapy to be an acceptable alternative to radiotherapy. Of note, the outcomes for patients treated with standard radiotherapy in the Nordic trial were unexpectedly poor compared with those seen in the NOA-08 and ANOCEF trials. This discrepancy might reflect a problem with treatment adherence: 22% of patients randomized to the standard radiotherapy arm dropped out at 4 weeks, and nearly one-third of patients underwent treatment crossover. Although an issue, this likely reflects the challenges in treating these patients with radiotherapy and an inherent added benefit to using outpatient chemotherapy.

In the Nordic trial, temozolomide therapy was found to be particularly efficacious in patients with *MGMT* promoter methylation. In fact, patients in the Nordic trial with *MGMT* promoter methylation had better OS when treated with temozolomide than with radiotherapy, a finding corroborated by Reifenberger et al.[9] These findings were echoed by the ANOCEF TAG Trial, which found a median survival of 31 weeks in elderly patients with *MGMT* promoter methylation treated with temozolomide vs 18.7 weeks in patients without *MGMT* promoter methylation.[19] The *MGMT* status

Table 4. Effect of Treatment Modality and *MGMT* Promoter Methylation Status on Event-Free Survival

Source	Treatment	*MGMT* Promoter Methylation Status	Patients, No.	Median OS, mo (95% CI)	HR (95% CI)	*P* Value
Wick et al,[5] 2012 (NOA-08 trial)	Temozolomide	–	77	3.3 (3.0-3.5)	1.95 (1.41-2.69)[a]	.01
	Temozolomide	+	31	8.4 (5.5-11.7)	0.53 (0.33-0.86)[a]	.01
	Radiotherapy	–	59	4.6 (3.7-6.3)	1 [Reference][a]	
	Radiotherapy	+	42	4.6 (4.2-5.0)	1 [Reference][a]	
Malmström et al,[6] 2012 (Nordic trial)	Temozolomide	–	44	...		
	Temozolomide	+	28	...		
	Radiotherapy	–	68	...		
	Radiotherapy	+	63	...		
Reifenberger et al,[9] 2012 (German Glioma Network trial)	Chemotherapy[b]	–	2	0.5 (NA)[c]	...	
	Chemotherapy[b]	+	14	6.8 (2.5-11.0)	...	
	Radiotherapy	–	30	5.2 (4.3-6.2)	...	
	Radiotherapy	+	31	4.5 (3.5-5.4)	...	

Abbreviations: HR, hazard ratio; *MGMT*, O^6-methylguanine-DNA-methyltransferase gene; NA, not applicable; OS, overall survival; ellipses, not reported; –, negative, +, positive.

[a] The HR was calculated relative to radiotherapy using both tumors with *MGMT* promoter methylation and those without *MGMT* promoter methylation.

[b] Includes 14 patients treated with temozolomide, 1 patient treated with procarbazine hydrochloride plus lomustine, and 1 patient treated with nitrosourea alone.

[c] Analysis was limited by the small sample size for this treatment (n = 2).

had no effect on OS in patients treated with radiotherapy in either the Nordic trial or the NOA-08 trial. Importantly, monotherapy with either radiotherapy or chemotherapy is superior to supportive care alone.

In a recent meta-analysis, Yin et al[20] analyzed all studies, including those with lower levels of evidence, comparing temozolomide vs radiotherapy for elderly patients with GBM. The authors found a longer OS in the temozolomide group compared with the radiotherapy group. However, when only level 1 evidence was included in the analysis (the Nordic and NOA-08 trials), the authors could only conclude that temozolomide was not inferior to radiotherapy. This meta-analysis supports the idea that temozolomide alone is an effective treatment option. There have also been several single-arm trials studying the role of temozolomide and radiotherapy in the care of elderly patients with GBM, which we have summarized in eTable 1 and eTable 2 in the Supplement. From these studies, we can conclude that temozolomide alone is an effective treatment option in elderly patients with *MGMT* promoter methylation as compared with patients without *MGMT* methylation. Unfortunately, the ongoing EORTC-NCIC Intergroup Trial (EORTC 26062-22061/NCIC CE.6), which has been designed to study radiotherapy alone (40 Gy in 15 fractions) vs chemoradiation (40 Gy in 15 fractions concurrent with standard daily temozolomide dosing and 6 months of adjuvant temozolomide) in elderly patients, will not offer further insight into the question of chemotherapy alone for this patient cohort.

While chemoradiation with temozolomide has become the standard of care for the treatment of young patients with GBM, the value of this treatment to elderly patients remains unclear. In the EORTC-NCIC trial, the benefit of chemoradiation appeared to wane in patients older than 65 years; in this cohort, median survival was 12.0 months with radiotherapy alone vs 10.9 months in patients treated with radiotherapy and temozolomide. Interestingly, Minniti et al[21] found an overall survival of 10.6 months in patients older than 70 years treated with standard radiotherapy with concomitant and adjuvant temozolomide, but survival of 12.4 months in a second elderly cohort treated with hypofractionated radiotherapy with concomitant temozolomide.[22] The shortcomings of chemoradiation with standard radiotherapy in elderly patients could speak to a difference in the biology of the disease in this cohort.[23] Conversely, this shortcoming could reflect a lack of physiological reserve needed to tolerate treatment, a greater burden of associated medical comorbidities that could worsen its undesired effects, or less aggressive surgery. If so, chemoradiation may be the best available therapy in elderly patients who have good physiological reserve and have undergone aggressive surgical resection. Furthermore, the role of bevacizumab in the elderly population is yet to be understood. Recent studies evaluating concurrent chemoradiation with temozolomide and bevacizumab in younger patients newly diagnosed as having GBM[24,25] have not shown an OS advantage, and the high incidence of associated adverse events speaks against its likely benefit in elderly patients. The efficacy of bevacizumab with radiotherapy in elderly patients is being explored (clinicaltrials.gov identifier: NCT01443676), but the failure of early bevacizumab with standard therapy to improve OS raises questions regarding the rationale for further study.

The role of surgery in elderly patients remains unclear, although paradoxically, the value of surgical resection in this population may be even greater than in younger patients. This is because of the often attenuated role of adjuvant therapies.[26] Extent of resection (complete vs incomplete vs biopsy) was found to be an independent prognostic factor for OS in the multivariate Cox analysis in the NOA-08 trial. A small randomized trial conducted in the pretemozolomide era also found improved OS at 3 months in elderly patients who underwent a gross total or subtotal resection as compared with biopsy alone (5.6 vs 2.8 months, respectively), although these findings may have been compromised by an imbalance in prognostic factors between the 2 arms.[27] Lastly, surgical resection has been found to confer a survival advantage to biopsy alone in elderly patients in multiple retrospective studies.[26,28,29] At this time, we would recommend maximal safe resection in elderly patients.

There are several limitations associated with our recommendations. First, the data allowing comparison of temozolomide alone with radiotherapy alone in elderly patients with GBM is limited. While the literature contains 2 randomized trials, more studies are needed to further define outcomes from each of these treatment options. Second, the literature has a lack of coherence in the definition of *elderly*. Third, the dosage and duration of temozolomide used and the dosage and modality of radiotherapy used are not consistent from study to study. This heterogeneity complicates interpretation of the data and compromises the approach of data pooling for meta-analysis. Lastly, elderly patients who have had an optimal surgical resection of a tumor with *MGMT* promotor methylation and have a Karnofsky Performance Status score higher than 70 should be considered for radiotherapy with concurrent chemoradiation, per the trial by Stupp and colleagues.

Box. Recommendations

Level 1A
- Either single-agent temozolomide or hypofractionated radiotherapy alone may be used for the treatment of elderly patients with glioblastoma multiforme who are not candidates to receive combined radiotherapy and chemotherapy.

Level 1B
- Elderly patients whose tumors have methylation of the O^6-methylguanine-DNA-methyltransferase gene (*MGMT*) promoter are likely to receive the greatest benefit from temozolomide alone over radiotherapy.
- There is insufficient evidence to recommend either temozolomide alone or radiotherapy alone in patients without *MGMT* promoter methylation. Treatment should be individualized to the patient.

Conclusions

Based on the current body of high-level evidence, we conclude that single-agent temozolomide or hypofractionated radiotherapy alone is recommended for the treatment of elderly patients with GBM who are not candidates for combined chemoradiation as per the trial by Stupp and colleagues (**Box**). In addition, elderly patients whose tumors have *MGMT* promoter methylation are likely to receive the greatest benefit from temozolomide alone over radiotherapy. At this time, there is insufficient evidence to make a recommendation for either temozolomide or radiotherapy in patients without *MGMT* promoter methylation; however, our practice is to offer radiotherapy alone in this cohort.

ARTICLE INFORMATION

Published Online: March 30, 2015. doi:10.1001/jamaneurol.2014.3739.

Author Affiliations: Division of Neurosurgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Zarnett, Gosio, Das); Department of Radiation Oncology, Sunnybrook Hospital, University of Toronto, Toronto, Ontario, Canada (Sahgal); Department of Neurology, Sunnybrook Hospital, University of Toronto, Toronto, Ontario, Canada (Perry); Department of Neurological Surgery, University of California, San Francisco (Berger, Chang); Keenan Research Centre for Biomedical Science, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Das); Arthur and Sonia Labatt Brain Tumour Research Centre, University of Toronto, Toronto, Ontario, Canada (Das).

Author Contributions: Dr Das had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sahgal, Das.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Zarnett, Sahgal, Gosio, Das.
Critical revision of the manuscript for important intellectual content: Zarnett, Sahgal, Perry, Berger, Chang, Das.
Statistical analysis: Zarnett, Das.
Obtained funding: Das.
Study supervision: Zarnett, Sahgal, Chang, Das.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Das is supported by the Canadian Cancer Society Research Institute. Mr Zarnett is supported by the Comprehensive Research Experience for Medical Students Award from the University of Toronto.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Kevin Thorpe, MMath, Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada, reviewed the articles to determine the level of evidence accrued; he received no compensation.

REFERENCES

1. Holdhoff M, Chamberlain MC. Controversies in the treatment of elderly patients with newly diagnosed glioblastoma. *J Natl Compr Canc Netw*. 2013;11(9):1165-1172.

2. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol*. 2012;14(suppl 5):v1-v49.

3. Sijben AE, McIntyre JB, Roldán GB, et al. Toxicity from chemoradiotherapy in older patients with glioblastoma multiforme. *J Neurooncol*. 2008;89(1):97-103.

4. Kita D, Ciernik IF, Vaccarella S, et al. Age as a predictive factor in glioblastomas: population-based study. *Neuroepidemiology*. 2009;33(1):17-22.

5. Wick W, Platten M, Meisner C, et al; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol*. 2012;13(7):707-715.

6. Malmström A, Grønberg BH, Marosi C, et al; Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol*. 2012;13(9):916-926.

7. Weller M, Stupp R, Reifenberger G, et al. *MGMT* promoter methylation in malignant gliomas: ready for personalized medicine? *Nat Rev Neurol*. 2010;6(1):39-51.

8. DeVries JG, Berlet GC. Understanding levels of evidence for scientific communication. *Foot Ankle Spec*. 2010;3(4):205-209.

9. Reifenberger G, Hentschel B, Felsberg J, et al; German Glioma Network. Predictive impact of *MGMT* promoter methylation in glioblastoma of the elderly. *Int J Cancer*. 2012;131(6):1342-1350.

10. Keime-Guibert F, Chinot O, Taillandier L, et al; Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. *N Engl J Med*. 2007;356(15):1527-1535.

11. Stupp R, Hegi ME, Mason WP, et al; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459-466.

12. Rønning PA, Helseth E, Meling TR, Johannesen TB. A population-based study on the effect of temozolomide in the treatment of glioblastoma multiforme. *Neuro Oncol*. 2012;14(9):1178-1184.

13. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol*. 1990;8(7):1277-1280.

14. Bjordal K, de Graeff A, Fayers PM, et al; EORTC Quality of Life Group. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. *Eur J Cancer*. 2000;36 (14):1796-1807.

15. Taphoorn MJ, Claassens L, Aaronson NK, et al; EORTC Quality of Life Group, and Brain Cancer, NCIC and Radiotherapy Groups. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer*. 2010;46(6):1033-1040.

16. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.

17. Darefsky AS, King JT Jr, Dubrow R. Adult glioblastoma multiforme survival in the temozolomide era: a population-based analysis of Surveillance, Epidemiology, and End Results registries. *Cancer*. 2012;118(8):2163-2172.

18. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol*. 2004;22(9):1583-1588.

19. Gállego Pérez-Larraya J, Ducray F, Chinot O, et al. Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial. *J Clin Oncol*. 2011; 29(22):3050-3055.

20. Yin AA, Cai S, Dong Y, et al. A meta-analysis of temozolomide versus radiotherapy in elderly glioblastoma patients. *J Neurooncol*. 2014;116(2): 315-324.

21. Minniti G, De Sanctis V, Muni R, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma in elderly patients. *J Neurooncol*. 2008;88(1):97-103.

22. Minniti G, De Sanctis V, Muni R, et al. Hypofractionated radiotherapy followed by adjuvant chemotherapy with temozolomide in elderly patients with glioblastoma. *J Neurooncol*. 2009;91(1):95-100.

23. Batchelor TT, Betensky RA, Esposito JM, et al. Age-dependent prognostic effects of genetic alterations in glioblastoma. *Clin Cancer Res*. 2004; 10(1, pt 1):228-233.

24. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370 (8):699-708.

25. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014; 370(8):709-722.

26. Ewelt C, Goeppert M, Rapp M, Steiger HJ, Stummer W, Sabel M. Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. *J Neurooncol*. 2011;103(3):611-618.

27. Vuorinen V, Hinkka S, Färkkilä M, Jääskeläinen J. Debulking or biopsy of malignant glioma in elderly people: a randomised study. *Acta Neurochir (Wien)*. 2003;145(1):5-10.

28. Chaichana KL, Chaichana KK, Olivi A, et al. Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival: clinical article. *J Neurosurg*. 2011;114(3):587-594.

29. Patwardhan RV, Shorter C, Willis BK, et al. Survival trends in elderly patients with glioblastoma multiforme: resective surgery, radiation, and chemotherapy. *Surg Neurol*. 2004;62(3):207-213.