ORIGINAL ARTICLE

# Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

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## ABSTRACT

### BACKGROUND

Glioblastoma is associated with a poor prognosis in the elderly. Survival has been shown to increase among patients 70 years of age or younger when temozolomide chemotherapy is added to standard radiotherapy (60 Gy over a period of 6 weeks). In elderly patients, more convenient shorter courses of radiotherapy are commonly used, but the benefit of adding temozolomide to a shorter course of radiotherapy is unknown.

### METHODS

We conducted a trial involving patients 65 years of age or older with newly diagnosed glioblastoma. Patients were randomly assigned to receive either radiotherapy alone (40 Gy in 15 fractions) or radiotherapy with concomitant and adjuvant temozolomide.

### RESULTS

A total of 562 patients underwent randomization, 281 to each group. The median age was 73 years (range, 65 to 90). The median overall survival was longer with radiotherapy plus temozolomide than with radiotherapy alone (9.3 months vs. 7.6 months; hazard ratio for death, 0.67; 95% confidence interval [CI], 0.56 to 0.80; P<0.001), as was the median progression-free survival (5.3 months vs. 3.9 months; hazard ratio for disease progression or death, 0.50; 95% CI, 0.41 to 0.60; P<0.001). Among 165 patients with methylated $O^6$-methylguanine–DNA methyltransferase (MGMT) status, the median overall survival was 13.5 months with radiotherapy plus temozolomide and 7.7 months with radiotherapy alone (hazard ratio for death, 0.53; 95% CI, 0.38 to 0.73; P<0.001). Among 189 patients with unmethylated MGMT status, the median overall survival was 10.0 months with radiotherapy plus temozolomide and 7.9 months with radiotherapy alone (hazard ratio for death, 0.75; 95% CI, 0.56 to 1.01; P=0.055; P=0.08 for interaction). Quality of life was similar in the two trial groups.

### CONCLUSIONS

In elderly patients with glioblastoma, the addition of temozolomide to short-course radiotherapy resulted in longer survival than short-course radiotherapy alone. (Funded by the Canadian Cancer Society Research Institute and others; ClinicalTrials.gov number, NCT00482677.)

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Glioblastoma is a fatal illness that is associated with a median survival of less than 2 years. Population studies of glioblastoma have shown that survival declines with increasing age,[1,2] and the incidence of glioblastoma is increasing, especially among the elderly.[3] Older patients have been underrepresented in most randomized trials, in which the average age of participants is approximately 55 years, as compared with the population-based median for patients with glioblastoma of 65 years of age.[2] In 2005, a phase 3 trial of radiotherapy alone (60 Gy over a period of 6 weeks) versus radiotherapy plus temozolomide showed longer survival with the combination.[4] However, that trial included only patients 70 years of age or younger. Exploratory analyses have suggested less effect from the addition of temozolomide with increasing age, with less survival benefit among patients 65 to 70 years of age (hazard ratio for death, 0.78; 95% confidence interval [CI], 0.50 to 1.24; P=0.29) than among younger patients.[2]

Management of glioblastoma in patients 65 years of age or older is difficult given the poor prognosis, frequent coexisting conditions, and an increased risk of toxic effects from radiotherapy on the aging brain[5]; however, phase 3 studies have shown the effectiveness of shorter courses of radiotherapy as compared with supportive care alone[6] or standard radiotherapy (60 Gy over a period of 6 weeks).[7] There is also evidence that temozolomide alone may be more effective than radiotherapy alone for elderly patients with methylation of the $O^6$-methylguanine–DNA methyltransferase (MGMT) gene promoter region.[8] Although the incidence of MGMT promoter methylation is not age-dependent, data are lacking with respect to the benefit of adding temozolomide to short-course radiotherapy in elderly patients with glioblastoma and its dependence on status regarding MGMT promoter methylation in tumors (MGMT status).[5,9,10] We tested whether a new chemoradiation strategy for elderly patients with glioblastoma would confer a survival advantage over short-course radiotherapy alone, especially among patients with methylated MGMT status.

## METHODS

### TRIAL OVERSIGHT

Each participating center obtained approval from the local ethics board, and each patient provided written informed consent. All data were collected and maintained by the Canadian Cancer Trials Group (CCTG) in Kingston, Ontario. The trial was sponsored in Canada by the CCTG, in Europe by the European Organisation for Research and Treatment of Cancer (EORTC), and in Australia and New Zealand by the Trans Tasman Radiation Oncology Group. Trial medication was supplied by Schering-Plough (now Merck), which had no role in the design of the trial, the collection or analysis of data, or the preparation of the manuscript. The trial was designed by the cochairs of the cooperative groups, and the first draft of the manuscript was prepared by the first author without writing assistance. All the authors participated in the preparation of the manuscript and the decision to submit it for publication, and all vouch for the accuracy and completeness of the data and for adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org.

### KEY ELIGIBILITY CRITERIA

This randomized, phase 3 trial enrolled patients 65 years of age or older who had newly diagnosed glioblastoma (World Health Organization grade IV astrocytoma), which was histologically confirmed after surgery or biopsy performed less than 28 days before randomization. Patients were deemed by their physicians not to be suitable to receive conventional radiotherapy (60 Gy in 30 fractions over a period of 6 weeks) in combination with temozolomide. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (on a scale ranging from 0 to 4, with higher values indicating greater disability) and were receiving glucocorticoids at a stable or decreasing dose. Adequate hematologic, renal, and hepatic function, as specified in the protocol, was required. Protocol treatment began within 2 weeks after randomization.

### TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive either radiotherapy alone or radiotherapy plus temozolomide. Radiation was planned with the use of three-dimensional planning systems for a total dose of 40.05 Gy, administered in 15 daily fractions over a period of 3 weeks. Concurrent temozolomide was administered with radiotherapy at a dose of 75 mg per square meter of body-surface area per day for 21 consecutive days from day 1 until the final day of radiotherapy. Adjuvant temozolomide was administered

at a dose of 150 to 200 mg per square meter per day for 5 consecutive days of a 28-day cycle for up to 12 cycles or until disease progression. Use of antiemetic and infection prophylaxis was at the discretion of the investigator.

### RADIOTHERAPY QUALITY ASSURANCE

The procedure for radiotherapy quality assurance involved a single dry-run case from each center that was reviewed by the chair of radiotherapy quality assurance. If a dry run was deemed unsatisfactory, enrollment at that center was suspended until acceptable changes were made. The gross tumor volume was defined as the contrast-enhancing volume on the postsurgical planning magnetic resonance imaging (MRI) scan and included the surgical bed. The clinical target volume was a 1.5-cm margin respecting anatomical boundaries beyond the gross-tumor-volume contour, and a planning target volume margin of 0.5 cm was applied. Planning specifications are provided in the trial protocol.

### PATIENT EVALUATION AND FOLLOW-UP

Local pathological diagnosis was accepted, with a requirement for provision of tissue for central histologic review and assessment of MGMT status. Baseline tests included neurologic examination, Mini–Mental State Examination (MMSE; scores range from 0 to 30, with higher scores indicating better cognitive function), and MRI. Follow-up requirements were identical for both groups. Quality-of-life instruments were administered weekly on day 1 of weeks 1, 2, and 3 during radiotherapy, then 1 week after the last day of radiotherapy, and then every 3 months until disease progression. The instruments were the EORTC Quality of Life Questionnaire–Core 30 (QLQ-C30) and the EORTC brain module (QLQ-BN20). The QLQ-C30 has five function domains (physical, role [work and household activities], emotional, cognitive, and social) and three symptom domains (fatigue, nausea and vomiting, and pain). It also includes five single-symptom domains (dyspnea, sleep, appetite, constipation, and diarrhea) and a global assessment domain. The QLQ-BN20 has four brain-cancer symptom clusters (visual, motor, communication, and uncertainty about the future) in addition to seven disease and treatment assessments (headache, seizures, drowsiness, hair loss, itching skin, leg weakness, and trouble controlling bladder function). For each function domain and symptom item, a linear transformation was applied to standardize the raw score to a range of 0 to 100. Full details of the analytic methods are in the Supplementary Appendix, available at NEJM.org.

### PATHOLOGICAL REVIEW AND MGMT DETERMINATION

Central pathological review was mandatory. Formalin-fixed, paraffin-embedded sections of tissue blocks or tumor microarrays were subject to immunohistochemical staining for isocitrate dehydrogenase mutation with anti–IDH1 R132H antibody, as described in the Supplementary Appendix. Methylation status of the MGMT gene promoter region was tested as described previously[11]; testing was performed retrospectively, with the evaluators unaware of the treatment assignments and outcome data. (For details of the analysis, see the Supplementary Appendix.)

### DETERMINATION OF DISEASE PROGRESSION

Progressive disease was defined as objective (radiologic) progression. For patients with complete resections at trial entry, progressive disease was defined as recurrent contrast-enhancing tumor detected on subsequent brain imaging. For patients with measurable disease at trial entry, progressive disease was defined as a new lesion or an increase by 25% or more in the estimated tumor area (two perpendicular diameters). Because early contrast enhancement can occur in at least the first 3 months after radiotherapy, the protocol anticipated cases of pseudoprogression. If brain imaging could not be performed, symptomatic progression was used to define progression. Symptomatic progressive disease was defined as a deterioration in health in the absence of both radiologic progression and clinical explanations other than true progressive disease (e.g., seizures, stroke, or toxic effects of anticonvulsant agents). The determination of deterioration in health was at the discretion of the local principal investigator, but radiologic confirmation was strongly recommended and symptomatic progressive disease was used only when imaging could not be performed. The date of progressive disease was defined as the first time that the criteria were met.

### STATISTICAL ANALYSIS

The primary end point was overall survival, measured from the date of randomization until death or censoring at the last day that the patient was

known to be alive. Progression-free survival was measured from the date of randomization until disease progression or death (if no progression was reported) or until the last evaluation date. We used the log-rank test adjusted for the stratification factors at randomization to test for differences in overall and progression-free survival.

We calculated that at least 520 events (deaths) would be required for the trial to have 90% power to detect a hazard ratio of 0.75 (median overall survival of 8 months with radiotherapy plus temozolomide vs. 6 months with radiotherapy alone), at a two-sided 5% level. Treatment assignment was performed centrally with the randomization algorithm dynamically minimizing the chance of an imbalance between trial groups with respect to the following stratification factors: center, ECOG performance status (0 or 1 vs. 2), age group (65 to 70 years vs. 71 to 75 years vs. ≥76 years), and extent of resection (biopsy only vs. partial or complete resection). A single interim analysis of overall survival to assess futility was planned when 120 events (deaths) had occurred; the two-stage stopping rule of Ellenberg and Eisenberger was used.[12] Final analysis populations included the intention-to-treat population (all randomly assigned patients) for all efficacy end points and the as-treated population (all patients who received at least one dose of trial treatment) for safety and drug-exposure analyses.

## RESULTS

### PATIENT CHARACTERISTICS

Patients underwent randomization from November 2007 through September 2013. The prespecified interim analysis occurred in April 2011, and the independent data and safety monitoring committee recommended continuation. After the number of prespecified events was reached, the last evaluation date for data was March 3, 2015, and the final database was locked for analysis on March 1, 2016. All 562 randomly assigned patients (281 in each group) were included in the intention-to-treat analysis, including 3 patients who did not receive the assigned intervention (2 assigned to radiotherapy plus temozolomide and 1 assigned to radiotherapy alone) (Fig. 1). Almost all the patients were followed until they died: 263 (93.6%) assigned to radiotherapy plus temozolomide and 272 (96.8%) assigned to radiotherapy alone. For the small group of patients

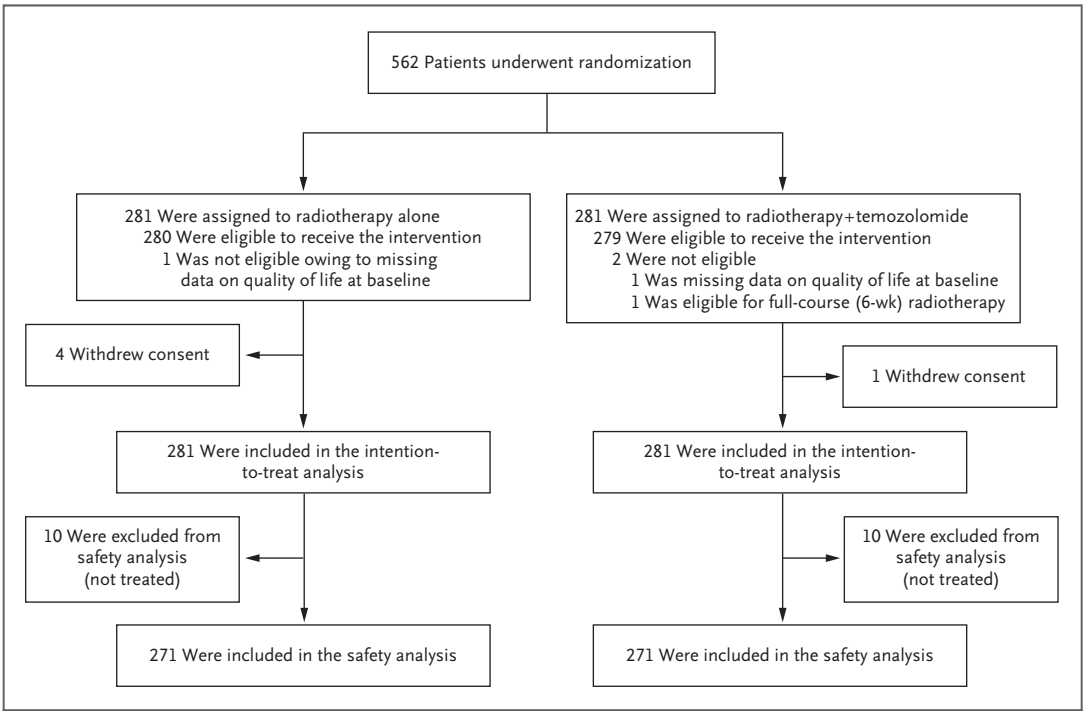


**Figure 1. Randomization, Treatment, and Follow-up.**

who remained alive, the median follow-up was 17 months. The median age was 73 years (range, 65 to 90), with 29.5% of the patients older than 75 years of age. A total of 61.0% of the participants were men; the ECOG performance status was 0 or 1 in 76.9%, and 68.3% of the participants underwent partial or complete surgical resection. Baseline characteristics and stratification variables were well balanced between the two groups (Table 1).

### CENTRAL PATHOLOGICAL REVIEW

Tissue samples from 515 of the 562 randomly assigned patients (91.6%) were received at the

**Table 1. Baseline Demographic and Clinical Characteristics According to Treatment Group.***

| Characteristic | Radiotherapy Alone (N=281) | Radiotherapy plus Temozolomide (N=281) | Total (N=562) |
|---|---|---|---|
| Sex — no. (%) | | | |
| Female | 109 (38.8) | 110 (39.1) | 219 (39.0) |
| Male | 172 (61.2) | 171 (60.9) | 343 (61.0) |
| Age — no. (%) | | | |
| 65–70 yr | 82 (29.2) | 83 (29.5) | 165 (29.4) |
| 71–75 yr | 114 (40.6) | 117 (41.6) | 231 (41.1) |
| ≥76 yr | 85 (30.2) | 81 (28.8) | 166 (29.5) |
| MMSE score† | | | |
| No. of patients analyzed | 270 | 272 | 542 |
| Median score | 27.0 | 27.0 | 27.0 |
| ECOG performance status — no. (%)‡ | | | |
| 0 | 57 (20.3) | 74 (26.3) | 131 (23.3) |
| 1 | 160 (56.9) | 141 (50.2) | 301 (53.6) |
| 2 | 64 (22.8) | 66 (23.5) | 130 (23.1) |
| Taking glucocorticoids — no. (%) | | | |
| No | 67 (23.8) | 72 (25.6) | 139 (24.7) |
| Yes | 214 (76.2) | 209 (74.4) | 423 (75.3) |
| Extent of surgical resection — no. (%) | | | |
| Biopsy only | 89 (31.7) | 89 (31.7) | 178 (31.7) |
| Partial or complete resection | 192 (68.3) | 192 (68.3) | 384 (68.3) |
| MGMT status — no./total no. (%) | | | |
| Methylated | 77/173 (44.5) | 88/181 (48.6) | 165/354 (46.6) |
| Unmethylated | 96/173 (55.5) | 93/181 (51.4) | 189/354 (53.4) |
| Geographic region — no. (%)§ | | | |
| Europe | 125 (44.5) | 124 (44.1) | 249 (44.3) |
| Canada | 98 (34.9) | 101 (35.9) | 199 (35.4) |
| Australia and New Zealand | 49 (17.4) | 48 (17.1) | 97 (17.3) |
| Japan | 9 (3.2) | 8 (2.8) | 17 (3.0) |

* There were no significant differences between the trial groups. MGMT denotes $O^6$-methylguanine–DNA methyltransferase.
† Scores of the Mini–Mental State Examination (MMSE) range from 0 to 30, with higher scores indicating better cognitive function.
‡ The performance status on the Eastern Cooperative Oncology Group (ECOG) scale ranges from 0 to 4, with higher values indicating greater disability.
§ The trial was sponsored in Europe by the European Organization for Research and Treatment of Cancer, in Canada by the Canadian Cancer Trials Group, and in Australia and New Zealand by the Trans Tasman Radiation Oncology Group.

central laboratory. Twelve of the 515 tissue samples were nondiagnostic owing to a paucity of nonnecrotic tissue. Among the 503 samples examined centrally, glioblastoma was confirmed in 480 (95.4%), high-grade glioma in 15 (3.0%), diffuse glioma lacking high-grade features in 5 (1.0%), and anaplastic oligodendroglioma in 3 (0.6%). Immunohistochemical staining for the IDH-1 R132H mutation was positive in only 4 of the 481 specimens that were suitable for analysis.

**Table 2. Hematologic Toxic Effects.**

| Toxic Effect and Worst Reported Grade* | Radiotherapy Alone | Radiotherapy plus Temozolomide |
|---|---|---|
| | *no. of patients/total no. (%)* | |
| Anemia | | |
| 4 | 0/258 | 1/270 (0.4) |
| 3 | 0/258 | 2/270 (0.7) |
| 2 | 6/258 (2.3) | 20/270 (7.4) |
| 1 | 123/258 (47.7) | 188/270 (69.6) |
| 0 | 129/258 (50.0) | 59/270 (21.9) |
| Leukopenia | | |
| 4 | 0/258 | 6/270 (2.2) |
| 3 | 1/258 (0.4) | 13/270 (4.8) |
| 2 | 1/258 (0.4) | 29/270 (10.7) |
| 1 | 8/258 (3.1) | 38/270 (14.1) |
| 0 | 248/258 (96.1) | 184/270 (68.1) |
| Lymphopenia | | |
| 4 | 3/253 (1.2) | 16/268 (6.0) |
| 3 | 23/253 (9.1) | 57/268 (21.3) |
| 2 | 51/253 (20.2) | 92/268 (34.3) |
| 1 | 30/253 (11.9) | 45/268 (16.8) |
| 0 | 146/253 (57.7) | 58/268 (21.6) |
| Neutropenia | | |
| 4 | 1/249 (0.4) | 14/266 (5.3) |
| 3 | 1/249 (0.4) | 8/266 (3.0) |
| 2 | 2/249 (0.8) | 15/266 (5.6) |
| 1 | 5/249 (2.0) | 27/266 (10.2) |
| 0 | 240/249 (96.4) | 202/266 (75.9) |
| Thrombocytopenia | | |
| 4 | 1/257 (0.4) | 14/270 (5.2) |
| 3 | 0/257 | 16/270 (5.9) |
| 2 | 4/257 (1.6) | 21/270 (7.8) |
| 1 | 43/257 (16.7) | 123/270 (45.6) |
| 0 | 209/257 (81.3) | 96/270 (35.6) |

* Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

### TREATMENT ADHERENCE

Treatment adherence was high and, with respect to radiotherapy, did not differ significantly between trial groups. The median duration of radiotherapy was 3 weeks (15 fractions) and the median dose delivery was 40.05 Gy in both groups. The median duration of concomitant temozolomide was 21 days, as planned. The median number of adjuvant cycles delivered was five. A total of 11 of the 281 patients assigned to radiotherapy plus temozolomide did not receive any protocol treatment. In all, 86 patients did not receive adjuvant temozolomide: 31 had symptomatic progression before adjuvant therapy, 25 had intercurrent illness, 11 had adverse effects related to temozolomide, 9 declined treatment, 8 died, 1 was not adherent to treatment, and 1 was removed after randomization and received a full course of radiotherapy plus temozolomide. After disease progression, 197 of 493 patients (40.0%) received other anticancer therapies, and the percentage of patients was similar in the two groups. As expected, temozolomide was more commonly used in the radiotherapy-alone group, and non-temozolomide systemic therapies were more commonly used in the radiotherapy-plus-temozolomide group. (For details, see the Supplementary Appendix.)

### TOXIC EFFECTS

Toxic effects were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0, and were as expected with temozolomide. As expected, radiotherapy plus temozolomide was associated with a slightly higher rate of adverse events than radiotherapy alone; the worst recorded hematologic toxic effects are listed in Table 2. The rates of grade 3 or 4 events were as follows: lymphopenia, 27.2% with radiotherapy plus temozolomide versus 10.3% with radiotherapy alone; thrombocytopenia, 11.1% versus 0.4%; and neutropenia, 8.3% versus 0.8%. Low-grade opportunistic infection was reported in 2 patients who received radiotherapy plus temozolomide, with no other significant between-group differences in reported infections. Serious adverse events leading to death were reported in 38 patients who received radiotherapy plus temozolomide and in 35 patients who received radiotherapy alone; two of these events in each group

were attributed by the investigators to treatment, with the rest due to disease progression.

### OVERALL SURVIVAL

The Kaplan–Meier estimates of median overall survival were 9.3 months with radiotherapy plus temozolomide and 7.6 months with radiotherapy alone (Fig. 2A). The risk of death was lower by 33% with radiotherapy plus temozolomide than with radiotherapy alone (hazard ratio, 0.67; 95% CI, 0.56 to 0.80; P<0.001). In Cox regression modeling with adjustment for baseline factors, radiotherapy plus temozolomide remained significantly better than radiotherapy alone with respect to overall survival, with an estimated hazard ratio of 0.67 (95% CI, 0.56 to 0.80; P<0.001). Baseline factors that correlated with overall survival included the extent of resection and MMSE score: patients with biopsy only had shorter survival than those with partial or complete resection (hazard ratio for death, 1.67; 95% CI, 1.38 to 2.02; P<0.001), and patients with higher MMSE scores had longer survival than those with lower scores (hazard ratio for death with a 1-unit increase as a

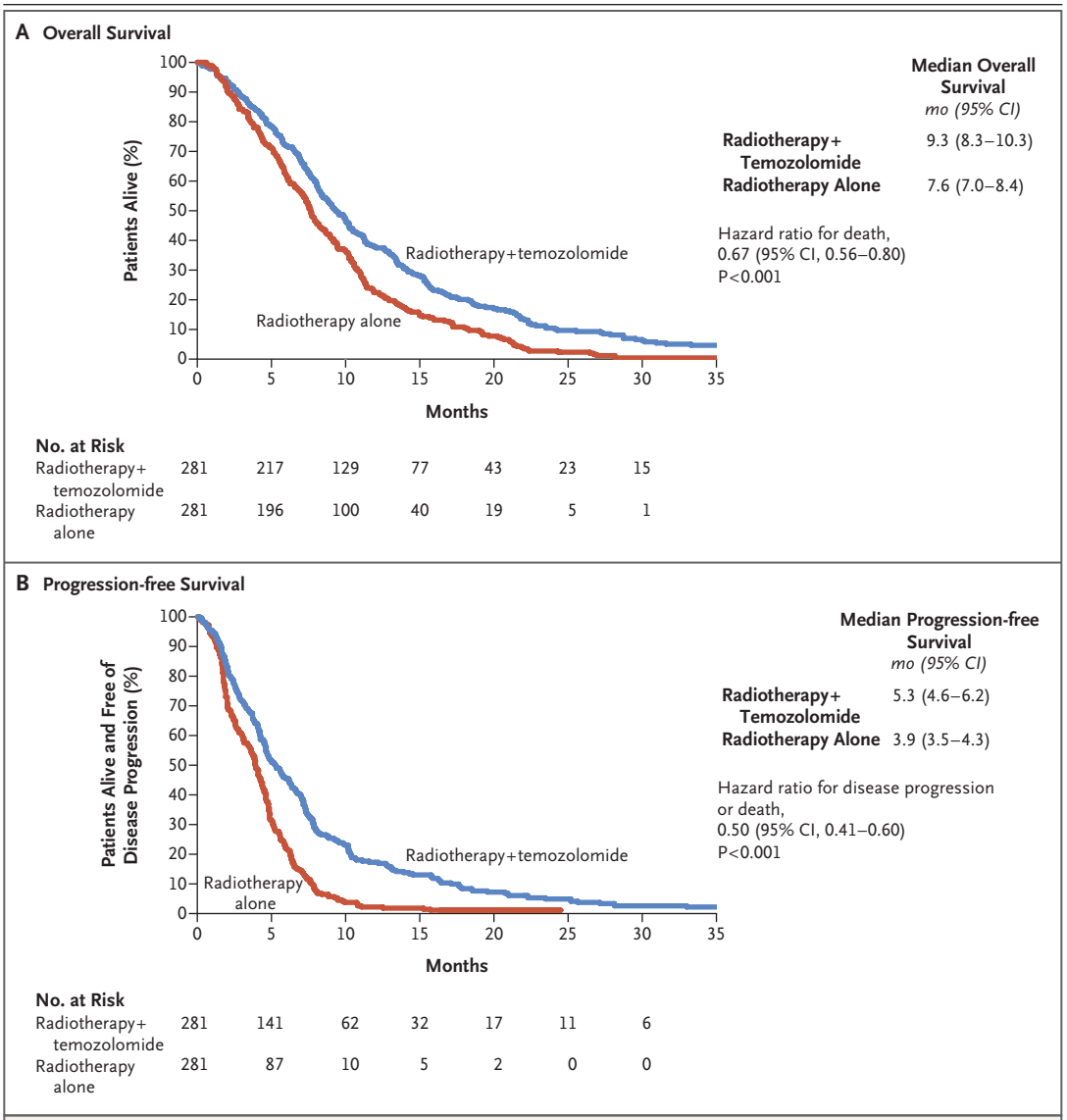


**Figure 2. Overall and Progression-free Survival According to Treatment Group.**
The P values are two-sided.

continuous variable, 0.96; 95% CI, 0.94 to 0.98; P<0.001).

In proportional-hazard models assessing the interaction between treatment and stratification factors, treatment effect appeared to increase marginally with age. Patients 65 to 70 years of age derived less benefit from the addition of temozolomide than those 71 to 75 years of age or 76 years of age or older (P=0.06 for interaction). Among patients 65 to 70 years of age, the median overall survival was 8.7 months with radiotherapy plus temozolomide and 8.3 months with radiotherapy alone (hazard ratio for death, 0.93; 95% CI, 0.68 to 1.27). Among patients 71 to 75 years of age, the median overall survival was 9.3 months versus 7.6 months (hazard ratio, 0.63; 95% CI, 0.48 to 0.83). Among patients 76 years of age or older, the median overall survival was 10.0 months versus 7.1 months (hazard ratio, 0.53; 95% CI, 0.38 to 0.73). No significant differences of treatment effect across levels of other stratification factors were observed. Exploratory analyses of overall survival at 12, 18, and 24 months favored radiotherapy plus temozolomide over radiotherapy alone at all time points (Table 3).

### PROGRESSION-FREE SURVIVAL

The median progression-free survival was 5.3 months with radiotherapy plus temozolomide as compared with 3.9 months with radiotherapy alone (hazard ratio for disease progression or death, 0.50; 95% CI, 0.41 to 0.60; P<0.001) (Fig. 2B). A Cox regression model adjusting for other baseline factors showed that radiotherapy plus temozolomide remained significantly better than radiotherapy alone with respect to progression-free survival (hazard ratio, 0.52; 95% CI, 0.43 to 0.63; P<0.001). Baseline factors that correlated with progression-free survival included the extent of resection and MMSE score; patients with biopsy only had shorter progression-free survival than those with partial or complete resection (hazard ratio, 1.45; 95% CI, 1.20 to 1.75; P<0.001), and patients with higher MMSE scores had longer progression-free survival than those with lower scores (hazard ratio with a 1-unit increase as a continuous variable, 0.97; 95% CI, 0.95 to 0.98; P<0.001). As with overall survival, younger age was associated with less benefit from treatment (hazard ratios, 0.76 [95% CI, 0.55 to 1.05] for patients 65 to 70 years of age vs. 0.42 [95% CI, 0.3 to 0.57] for patients 71 to 75 years of age vs. 0.49 [95% CI, 0.35 to 0.68] for patients ≥76 years of age; P=0.02).

### RESULTS ACCORDING TO MGMT STATUS

A total of 462 tissue samples were able to be evaluated in an MGMT gene promoter analysis, and MGMT results were successfully obtained from 354 samples (181 from patients assigned to radiotherapy plus temozolomide and 173 from patients assigned to radiotherapy alone). In the radiotherapy-alone group, MGMT status was not a prognostic factor (overall survival, 7.9 months with unmethylated status and 7.7 months with methylated status; hazard ratio for death with

**Table 3. Exploratory Analyses of Overall Survival Rate at 12, 18, and 24 Months According to Treatment Group and MGMT Status.**

| Population | At 12 Months | At 18 Months | At 24 Months |
|---|---|---|---|
| | | *percent (95% confidence interval)* | |
| All patients | | | |
| Radiotherapy alone | 22.2 (17.5–27.3) | 10.8 (7.4–14.8) | 2.8 (1.2–5.4) |
| Radiotherapy plus temozolomide | 37.8 (32.1–43.6) | 20.0 (15.5–24.9) | 10.4 (7.1–14.5) |
| Patients with unmethylated MGMT | | | |
| Radiotherapy alone | 21.3 (13.7–30.0) | 12.7 (6.9–20.3) | 3.8 (1.1–9.6) |
| Radiotherapy plus temozolomide | 32.3 (23.0–42.0) | 13.4 (7.3–21.2) | 6.7 (2.7–13.1) |
| Patients with methylated MGMT | | | |
| Radiotherapy alone | 29.9 (19.9–40.5) | 13.6 (7.0–22.4) | 4.1 (1.1–10.4) |
| Radiotherapy plus temozolomide | 55.7 (44.7–65.3) | 34.1 (24.4–44.0) | 17.8 (10.5–26.7) |

unmethylated status, 0.93; 95% CI, 0.68 to 1.21; P=0.64). As anticipated, MGMT status predicted longer survival with radiotherapy plus temozolomide than with radiotherapy alone. Although the greatest benefit was observed in patients with methylated MGMT status (median survival, 13.5 months with radiotherapy plus temozolomide vs. 7.7 months with radiotherapy alone; hazard ratio, 0.53; 95% CI, 0.38 to 0.73; P<0.001), a clinically meaningful overall survival advantage, which did not reach statistical significance, was also observed in patients with unmethylated MGMT status (median survival, 10.0 months vs. 7.9 months; hazard ratio, 0.75; 95% CI, 0.56 to 1.01; P=0.055; P=0.08 for interaction) (Fig. S19 and S20 in the Supplementary Appendix). In addition, a survival advantage was observed at 12, 18, and 24 months in patients with methylated MGMT status (Table 3).

### QUALITY OF LIFE

Baseline quality-of-life scores for symptom and function domains were similar in the two groups. Nausea and constipation were worse during chemoradiotherapy than during radiotherapy alone, but changes in the scores on all other symptom and function domains were similar in the two groups. We conducted further quality-of-life analyses using time to deterioration (with deterioration defined as a 10-point decrease in the score on the function domain or a 10-point increase in the score on the symptom domain) and plots of quality-of-life scores over time (Fig. S1 to S18 in the Supplementary Appendix). In this trial involving elderly patients with glioblastoma, disease progression occurred early, and the adherence rate for completion of instruments reported by the patient declined during the trial, as expected. Because the number of data points decreased over time, it is problematic to use more complex models for these analyses. As in the overall quality-of-life response analysis, only nausea and vomiting and constipation were associated with significant differences in time to deterioration (shorter in the radiotherapy-plus-temozolomide group than in the radiotherapy-alone group), and there was a significantly greater treatment-by-time interaction in the radiotherapy-plus-temozolomide group than in the radiotherapy-alone group for nausea and vomiting and constipation. There were no other clinically important differences between trial groups, which supports our observation that quality of life was similar in the two treatment groups.

## DISCUSSION

In this phase 3 trial, the addition of temozolomide to short-course radiotherapy was associated with significantly longer progression-free and overall survival than short-course radiotherapy alone among patients 65 years of age or older with newly diagnosed glioblastoma. In subgroup analyses, the benefit of chemoradiotherapy was particularly evident in patients with methylated MGMT status, in whom median survival with temozolomide added to short-course radiotherapy was nearly twice that with short-course radiotherapy alone, but benefit was also observed in patients with unmethylated MGMT status (P=0.055). The survival advantage of temozolomide was conferred without a sacrifice in quality of life and with manageable chemotherapy-related toxic effects.

There has been no clear standard of care for the treatment of glioblastoma in the elderly.[13] Practice patterns show less use of surgical resection, radiotherapy, and chemotherapy with increasing age.[14-16] However, elderly patients with glioblastoma have been shown to benefit from these treatments. One trial randomly assigned 85 patients 70 years of age or older (median, 73 years; range, 70 to 85) to either postoperative radiotherapy (50.4 Gy in 28 fractions) plus supportive care or supportive care alone.[6] Those who received radiotherapy plus supportive care had longer overall survival than those who received supportive care alone (median, 6.7 months vs. 3.9 months), with no significant differences in quality of life or in cognition. Shorter-course hypofractionated radiotherapy is commonly used in the elderly, because it appears to be at least as effective as longer-duration radiotherapy.[6,17,18] Indeed, in the Nordic Clinical Brain Tumour Study Group (NCBTSG) trial, patients 60 years of age or older who were randomly assigned to a longer course of radiotherapy had worse outcomes than those assigned to a shorter course of radiotherapy or temozolomide chemotherapy.[7] Adherence was worse in the group assigned to 6 weeks of radiotherapy; only 72 of 100 patients (72.0%) in that group, as compared with 93 of 98 (94.9%) in the hypofractionated radiotherapy group,

completed the assigned therapy. Dropout was usually due to clinical worsening or disease progression.

The use of chemotherapy in elderly patients with glioblastoma is associated with improved survival, especially in patients with MGMT methylated status.[19-22] The NOA-08 randomized trial compared temozolomide alone with 6 weeks of radiotherapy alone in patients 65 years of age or older with malignant glioma.[8] Overall survival was similar in the two groups (8.6 months with temozolomide and 9.6 months with radiotherapy). The longest survival was observed among patients with methylated MGMT status who were assigned to temozolomide alone. Similarly, in the NCBTSG trial, the median overall survival was 9.7 months among patients with methylated MGMT status who were assigned to the temozolomide group. Survival was similar among all patients assigned to temozolomide or short-course radiotherapy and was significantly longer than among patients assigned to 6-week radiotherapy (8.3 months with temozolomide, 7.5 months with short-course radiotherapy, and 6.0 months with 6-week radiotherapy).[7] Taken together with our results, these findings suggest that abbreviated radiotherapy schedules are effective and include the benefit of high completion rates and reduced treatment time for patients who often have short survival and limited mobility.

Given the detrimental effect of increasing age on survival in patients with glioblastoma, it is surprising that patients 70 years of age or younger appeared to benefit somewhat less than older patients in our trial. Our decision to include patients as young as 65 years of age was based on current practice in our centers and on the results of previous randomized studies suggesting less benefit of radiotherapy plus temozolomide in patients 65 to 70 years of age than in younger patients. We recognized that patients 65 to 70 years of age may still be offered a full 6-week course of radiotherapy plus temozolomide, so we deliberately included only patients who were deemed to be unfit for that schedule. Whether the patient met this criterion was determined on the basis of the considered opinion of the treating physician and patient preferences for care. It is therefore possible that our subgroup of patients 65 to 70 years of age was enriched with patients who were more likely to have worse outcomes. That said, we were unable to detect any significant differences between age subgroups in known prognostic factors, such as extent of resection, MGMT status, ECOG performance status, quality of life, or score on the MMSE.

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## APPENDIX

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## REFERENCES

1. Paszat L, Laperriere N, Groome P, Schulze K, Mackillop W, Holowaty E. A population-based study of glioblastoma multiforme. Int J Radiat Oncol Biol Phys 2001;51:100-7.
2. Laperriere N, Weller M, Stupp R, et al. Optimal management of elderly patients with glioblastoma. Cancer Treat Rev 2013; 39:350-7.
3. Ostrom QT, Gittleman H, Fulop J, et al. Central Brain Tumor Registry of the United States (CBTRUS) statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro Oncol 2015;17:Suppl 4: 1-62.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
5. Brandes AA, Franceschi E, Tosoni A, et al. Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: correlation with MGMT promoter methylation status. Cancer 2009; 115:3512-8.
6. Keime-Guibert F, Chinot O, Taillandier

L, et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527-35.
**7.** Malmström A, Grønberg BH, Marosi C, et al. 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;13:916-26.
**8.** Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012;13:707-15.
**9.** Minniti G, Salvati M, Arcella A, et al. Correlation between O6-methylguanine-DNA methyltransferase and survival in elderly patients with glioblastoma treated with radiotherapy plus concomitant and adjuvant temozolomide. J Neurooncol 2011;102:311-6.
**10.** Reifenberger G, Hentschel B, Felsberg J, et al. Predictive impact of MGMT promoter methylation in glioblastoma of the elderly. Int J Cancer 2012;131:1342-50.
**11.** Vlassenbroeck I, Califice S, Diserens AC, et al. Validation of real-time methylation-specific PCR to determine O6-methylguanine-DNA methyltransferase gene promoter methylation in glioma. J Mol Diagn 2008;10:332-7.
**12.** Ellenberg SS, Eisenberger MA. An efficient design for phase III studies of combination chemotherapies. Cancer Treat Rep 1985;69:1147-54.
**13.** Mason M, Laperriere N, Wick W, et al. Glioblastoma in the elderly: making sense of the evidence. Neuro Oncol Pract 2016;2:77-86.
**14.** Iwamoto FM, Reiner AS, Panageas KS, Elkin EB, Abrey LE. Patterns of care in elderly glioblastoma patients. Ann Neurol 2008;64:628-34.
**15.** Barnholtz-Sloan JS, Williams VL, Maldonado JL, et al. Patterns of care and outcomes among elderly individuals with primary malignant astrocytoma. J Neurosurg 2008;108:642-8.
**16.** Lowry JK, Snyder JJ, Lowry PW. Brain tumors in the elderly: recent trends in a Minnesota cohort study. Arch Neurol 1998;55:922-8.
**17.** Bauman GS, Gaspar LE, Fisher BJ, Halperin EC, Macdonald DR, Cairncross JG. A prospective study of short-course radiotherapy in poor prognosis glioblastoma multiforme. Int J Radiat Oncol Biol Phys 1994;29:835-9.
**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;22:1583-8.
**19.** Glantz M, Chamberlain M, Liu Q, Litofsky NS, Recht LD. Temozolomide as an alternative to irradiation for elderly patients with newly diagnosed malignant gliomas. Cancer 2003;97:2262-6.
**20.** Chinot OL, Barrie M, Frauger E, et al. Phase II study of temozolomide without radiotherapy in newly diagnosed glioblastoma multiforme in an elderly populations. Cancer 2004;100:2208-14.
**21.** Chamberlain MC, Chalmers L. A pilot study of primary temozolomide chemotherapy and deferred radiotherapy in elderly patients with glioblastoma. J Neurooncol 2007;82:207-9.
**22.** Laigle-Donadey F, Figarella-Branger D, Chinot O, et al. Up-front temozolomide in elderly patients with glioblastoma. J Neurooncol 2010;99:89-94.