# Management of Glioblastoma in the Elderly

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**Abstract**: The optimal management of elderly patients with glioblastoma multiforme (GBM) remains controversial, as no evidence-based standard of care exists for this unique subpopulation. These patients typically have a poor prognosis and high rates of treatment-related toxicities. Unfortunately, many elderly GBM patients are often excluded from clinical trials. Consequently, the role of chemoradiotherapy with temozolomide for elderly patients is unclear, and these patients are often treated with radiotherapy (RT) alone or palliative approaches following surgical diagnosis. However, there is emerging evidence that healthy and fit elderly patients may benefit from combined modality therapy, and aggressive therapy should be considered. Elderly patients with poor performance scores have historically been offered RT alone when treated, but preliminary data support the use of temozolomide as initial therapy. Moreover, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation appears to be a predictive marker of benefit from temozolomide. In the future, this molecular prognostic factor may be used clinically to guide therapeutic decision-making for some elderly GBM patients. Nevertheless, other factors that affect quality of life, such as number of trips to the hospital, number of ancillary tests, morbidity of treatment, and treatment costs to the patient and community should also be considered.

## Introduction

The optimal management of glioblastoma multiforme (GBM) in elderly patients is one of the most challenging and controversial issues in neuro-oncology. "Elderly" is a vague term that is based on chronologic, rather than physiologic, age. However, physiologic age, as estimated by body health and probable life expectancy, is a better predictor of health status and should be used as an indicator when identifying patients as "elderly."[1]

The prevalence of GBM increases with age. Among individuals aged 65–74 years and 75–84 years, the incidence is 13.27 and 14.49 per 100,000 person-years, respectively.[2] Moreover, the age-specific

incidence of GBM in elderly individuals has increased consistently over the past several decades. Between 1983 and 1990, there was a 5% per year increase in the incidence of malignant astrocytomas among patients older than 65 years in a review of 6 French cancer registries.[3] Similar trends have been noted in North America. A study of the Surveillance, Epidemiology and End Results (SEER) registry database of patients diagnosed with cancer between 1973 and 2000 showed an increase in the incidence of GBM, with the fastest increase occurring among elderly patients (≥70 years).[4]

Furthermore, the marked increase in life expectancy and the aging of the "Baby Boomer" generation have led to the rapid expansion of the population older than 65 years.[5] Approximately 50% of GBM cases occur in patients aged 65 years or older.[6] Therefore, a dramatic increase in the number of GBM patients older than 65 years is expected in the near future.

Despite these data, there remains a lack of clinical trials and evidence-based guidelines for the optimal treatment of elderly patients with GBM. Elderly patients are generally underrepresented in clinical trials because coexisting comorbidities, dismal prognosis, and perceived poor tolerance of treatment discourages recruitment and enrollment.[1] Consequently, many patients are not treated vigorously, and are offered only radiotherapy (RT) alone or palliative care. The following review discusses and summarizes the clinical experience thus far in the management of elderly patients with GBM.

## Patterns of Care in the Elderly

Several population-based surveys investigating patterns of care in elderly patients with GBM have shown that they are less likely to receive effective therapies.[7-9] In a review of the SEER registry, age was the most significant predictor of which treatment modality was used.[8] Advanced age was associated with lower odds of resection and a decrease in the likelihood of receiving RT or chemotherapy. Approximately 35% of patients did not receive any form of RT or chemotherapy. A similar pattern of practice was observed in Ontario, Canada.[9] Meanwhile, the benefits of treatment modalities used in younger patients have also been shown in patients older than 65 years. In a retrospective review, patients who received all 3 treatment modalities (cytoreductive surgery, RT, and chemotherapy) had a significantly better overall survival (OS) compared with patients who received fewer treatments. The median OS of patients who received all 3 treatment modalities was 15 months (95% confidence interval [CI], 12.8–17.3), compared with 4.5 months (95% CI, 4.0–5.5) for patients who received RT plus surgery and 1.8 months (95% CI, 0.8–2.8) for patients who received surgery alone. Age younger than 75 years and Karnofsky performance score (KPS) of 70 or higher were favorable prognostic factors for prolonged survival.[10] These findings were confirmed in a recent study of a population of veterans with GBM, which showed that patients who received all 3 treatment modalities did best; the findings remained true among patients aged 70 years and older, such that these patients had an OS similar to patients younger than 70 years.[11] It is important to note that all of these studies were retrospective and therefore prone to selection bias. Additionally, because more aggressive treatments are often not administered in patients with poor KPS and large tumors, such patients were not considered in the studies. The individual treatment modalities will now be discussed (Table 1).

## Treatment Modalities

### *Cytoreductive Surgery*

The extent of tumor resection is considered one of the strongest prognostic factors in the survival of younger patients with GBM.[12] Although the value of cytoreductive surgery in elderly patients is a controversial topic, new studies have illustrated its feasibility and survival benefit.[10,13-17] These studies are mostly retrospective. There was only 1 small, prospective, randomized clinical trial, in which 30 patients older than 65 years who had radiologic evidence of malignant glioma were randomized into 2 treatment groups: stereotactic biopsy or open craniotomy with tumor resection.[18] Craniotomy and debulking of the tumor resulted in a significantly longer survival (171 days vs 85 days, respectively).[18] A larger, retrospective review from the Memorial Sloan-Kettering Cancer Center studied 394 patients aged 65 years or older. Extent of resection had a significant impact on OS, with an adjusted hazard ratio (HR) of 0.5 for gross total resection versus 0.7 and 1.0 for partial resection and biopsy, respectively.[16] Similar results were also reported in a retrospective review from The Johns Hopkins Hospital.[17] In another single-center study, 361 patients with newly diagnosed GBM were evaluated; 146 patients (40.4%) were aged 65 years or older. The patients were categorized into 4 subgroups according to the extent of resection: biopsy, partial, subtotal, and complete. Extent of surgery in the elderly patients was significantly associated with survival. Partial resection was associated with substantially shorter survival when compared to subtotal and complete resection (11.4 months vs 16.1 and 17.7 months, respectively). Interestingly, there was no significant difference in PFS or OS between elderly versus younger patients undergoing tumor resection. In contrast, age conferred poor OS in the biopsy group.[13]

**Table 1.** Clinical Trials and Major Retrospective Studies in Elderly Patients With GBM

| Study | Design | Age | KPS Cut-Off | Therapy | N | Median OS (months) | HR |
|---|---|---|---|---|---|---|---|
| **Surgical Debulking** | | | | | | | |
| Iwamoto et al[16] | Retrospective | ≥65 | None | Gross total resection<br>Partial resection<br>Biopsy | 109<br>212<br>73 | | 0.5*<br>0.7*<br>1.0* |
| Chaichana et al[17] | Retrospective<br>Case-control | ≥65 | ≥70 | Resection<br>Biopsy | 40<br>40 | 5.7*<br>4.0* | |
| Oszvald et al[13] | Retrospective | ≥65 | None | Gross total resection<br>Subtotal resection<br>Partial resection<br>Biopsy | 19<br>26<br>35<br>66 | 17.7*<br>16.1*<br>11.4*<br>4.0* | |
| **Radiotherapy** | | | | | | | |
| Keime-Guibert et al[20] | Randomized | ≥70 | ≥70 | Supportive care + RT (50 Gy)<br>Supportive care | 39<br>42 | 7.3*<br>4.2* | 0.47* |
| Scott et al[21] | Retrospective<br>SEER registry | >70 | None | RT<br>No RT | 1,817<br>1,019 | | 0.43* |
| **Hypofractioned RT vs Standard RT** | | | | | | | |
| Roa et al[24] | Randomized | ≥60 | ≥50 | Standard RT (60 Gy in 30 fx)<br>Hfx RT (40 Gy in 15 fx) | 51<br>49 | 5.1<br>5.6 | 0.89 |
| Bauman et al[22] | Prospective<br>Single-arm | ≥65 | ≤50 | Hfx RT(30 Gy in 10 fx)<br>Supportive care (historical cohort)<br>Standard RT (historical cohort) | 29 | 6*<br>1<br>10 | |
| **Standard RT vs Concurrent RT With TMZ** | | | | | | | |
| Gerstein et al[27] | Retrospective | ≥65 | None | Concurrent therapy | 51 | 11.5 | |
| Minniti et al[29] | Prospective<br>Single-arm | ≥70 | ≥70 | Concurrent therapy | 32 | 10.6 | |
| **Concurrent Hfx With TMZ** | | | | | | | |
| Cao et al[31] | Retrospective | ≥60 | None | Concurrent therapy<br>Hfx RT(40 Gy in 15 fx) | 57<br>55 | 6.9<br>9.3 | |
| Minniti et al[32] | Phase II | ≥70 | ≥60 | Concurrent therapy | 71 | 12.4 | |
| **Single-Agent TMZ** | | | | | | | |
| Perez-Larraya et al[38] | Prospective<br>Phase II | ≥70 | <70 | TMZ | 70 | 6.2 | |
| Wick et al<br>(NOA-08 trial)[36] | Randomized<br>Phase III | >60 | ≥60 | TMZ (1 week off/1 week on)<br>Standard RT | 193<br>178 | 8.2<br>9.8 | 1.24 |
| Malmstrom et al[37] | Randomized<br>Phase III | >60 | ≥50 | Standard RT<br>Hfx RT (34 Gy in 10 Fx)<br>Single-agent TMZ | 100<br>123<br>119 | 6<br>7.5<br>8 | |

*Statistically significant.

fx=fractions; Hfx=hypofractionated; HR=hazard ratio; KPS=Karnofsky Performance Status; OS=overall survival; RT=radiotherapy; SEER=Surveillance, Epidemiology and End Results; TMZ=temozolomide.

These data suggest that cytoreductive surgery in elderly patients with good clinical status may yield clinical benefit. They also underline the importance of identifying the preoperative factors that can predict the benefit of surgery. In one study, KPS of less than 80, chronic obstructive pulmonary disease, motor deficit, language deficit, cognitive deficit, and tumor size greater than 4 cm were independently associated with decreased survival after cytoreductive surgery. Patients with 0–1 factors had significantly better OS than patients with 2–3 or 4–6 factors (9.2 months vs 5.5 and 4.4 months, respectively).[19]

### *Radiotherapy*

The value of RT in elderly patients has been confirmed by a randomized trial comparing RT (focal radiation in daily fractions of 1.8 Gy given 5 days per week, for a total dose of 50 Gy) plus supportive care versus supportive care alone.[20] RT resulted in modest but significant improvement in survival of newly diagnosed patients with anaplastic astrocytoma or GBM. Patients were at least 70 years of age and had a KPS of 70 or higher.[20] RT conferred a significant median survival benefit of 12.2 weeks (median OS, 29.1 weeks for the RT arm vs 16.9 weeks for the supportive care arm) and did not cause severe adverse events or further deterioration in the KPS, health-related quality of life (HRQoL), or cognitive functions.[20] A recent review of the SEER registry was consistent with previously reported benefits of this treatment modality. RT significantly improved cancer-specific survival in patients aged 70 years or older (HR, 0.43; 95% CI, 0.38–0.49) after adjusting for surgery, tumor size, sex, ethnicity, and age at diagnosis.[21]

Although the benefit of RT is well accepted, the optimal regimen has yet to be established. Several single-armed studies suggest that accelerated hypofractionated RT is well tolerated in elderly patients with poor KPS.[22,23] In a study of 29 patients aged 65 years and older with poor performance status (KPS ≤50), hypofractionated RT (total dose of 30 Gy in 10 fractions administered throughout 2 weeks) improved the median OS of treated patients compared with a historical cohort who received supportive care only (6 months vs 1 month, respectively). The authors of this study concluded that hypofractionated RT is well tolerated and provides effective palliation in elderly patients with poor performance status.[22]

The noninferiority of hypofractionated RT was addressed in a randomized study that compared the survival benefit of standard RT (60 Gy in 30 fractions administered throughout 6 weeks) with accelerated hypofractionated RT (40 Gy in 15 fractions administered throughout 3 weeks).[24] A total of 100 patients aged 60 years or older with a KPS of 50 or higher were randomly assigned to either treatment arm. The median survivals were similar in the 2 groups (5.1 months vs 5.6 months for the 6-week and 3-week treatment groups, respectively; HR, 0.89; $P$=.57).[24] Although there was no difference in HRQoL (as measured by the KPS), a lessened increment in post-treatment corticosteroid dosing was noted in the hypofractionated RT arm.[24] The results of this trial suggest that, in elderly patients, hypofractionated RT schedules can produce survival outcomes similar to conventional schedules, without incremental toxicity.

### *Concurrent Chemotherapy and Radiotherapy*

Results of the randomized European Organization for Research and Treatment of Cancer (EORTC) 26981/22981-NCIC CE3 trial have established RT with concurrent and adjuvant temozolomide (Temodar, Schering) as the standard of care for most GBM patients aged 70 years or younger.[25] However, in a subgroup analysis, concurrent therapy did not improve the median OS of patients who were older than 60.[26] Despite superior 2-year and 5-year survival rates in the concurrent arm compared with the RT arm (21.8% vs 5.7% and 6.6% vs 0%, respectively), a definitive conclusion from this observation was not possible due to a lack of statistical power for the subgroup analysis.[26]

Other small, single-institution studies have illustrated the feasibility and benefit of concurrent and adjuvant temozolomide chemotherapy and irradiation in the elderly.[16,27-30] In a retrospective review, 51 patients aged 65 years or older were treated with RT (total dose 60 Gy in 30 fractions) and concurrent temozolomide (75 mg/m$^2$ daily during RT treatment).[27] After completion of concurrent therapy, adjuvant temozolomide (150–200 mg/m$^2$ on days 1–5 every 28 days for 6 cycles) was administered in 10 patients. Median OS was 11.5 months, and median PFS was 5.5 months. Patients who had undergone complete cytoreductive surgery had favorable outcomes, with an OS of 27.4 months compared with 15.5 months for partial resection patients and 7.9 months for biopsy patients. Grade 3/4 hematologic and nonhematologic toxicities were limited to 7 (14%) and 14 (27%) cases, respectively.[27] Similar results were observed in a small, single-arm, prospective study of 32 patients aged 70 years or older with a KPS of 70 or higher. Patients were treated with RT and concurrent temozolomide followed by 6 cycles of adjuvant temozolomide.[29] The median OS and PFS for these patients were 10.6 months and 7 months, respectively.[29] Although these studies suggest a potential benefit of concurrent chemoradiotherapy in elderly patients with good performance status, further randomized trials with larger numbers of enrolled patients are required to draw a definitive conclusion.

The addition of temozolomide to hypofractionated RT has been the subject of several studies, and this

combination may become a reasonable treatment option for some elderly patients.[24,31,32] Although a recently published, retrospective review did not show any survival benefit by adding temozolomide to hypofractionated RT in elderly patients, another small, single-arm, phase II trial suggested possible benefit.[31,32] In a retrospective review of 112 patients aged 60 years or older who were treated with hypofractionated RT, the 57 patients who received concurrent temozolomide had a lower median OS compared with the 55 patients who received hypofractionated RT only (6.9 months vs 9.3 months, respectively). It is important to note that only 24 patients (42%) in the concurrent temozolomide arm had cytoreductive surgery, compared to 34 patients (62%) in the hypofractionated RT-only arm. Furthermore, out of 40 patients in the concurrent arm who received adjuvant temozolomide after concurrent therapy, only 11 patients completed the full 6 cycles of treatment. The authors suggested that shortened duration of overlap between the concurrent chemotherapy and RT in the hypofractionated schedule may be the explanation for the lack of survival benefit.[31] These findings are contradicted by the results of a phase II trial that evaluated the efficacy and safety of hypofractionated RT (total dose 40 Gy in 15 fractions administered throughout 3 weeks) with concurrent temozolomide (75 mg/m$^2$ daily), followed by 12 cycles of adjuvant temozolomide (150–200 mg/m$^2$ on days 1–5 every 28 days) in 71 patients aged 70 years or older with a KPS of 60 or higher. The median OS and PFS were 12.4 months and 6 months, respectively. Methylation of $O^6$-methylguanine-DNA-methyltransferase (MGMT) remained an important tumor characteristic and was the strongest prognostic factor associated with OS and PFS.[32]

Despite the encouraging results of these small studies, the optimal combination regimen of RT and temozolomide has yet to be determined. An ongoing, international, randomized phase III study led by the NCIC Clinical Trials Group aims to address this question.[33] GBM patients older than 65 years are being treated with hypofractionated RT (total dose of 40 Gy in 15 fractions) with or without additional temozolomide as part of the concurrent and adjuvant therapy.

### *Chemotherapy*

The role of single-agent chemotherapy has been evaluated in elderly patients with GBM. Previous studies with small numbers of elderly patients proposed the use of single-agent temozolomide as an appropriate first-line treatment.[34,35] A retrospective analysis demonstrated that there was no significant difference in median OS in patients who received temozolomide alone (150–200 mg/m$^2$ on days 1–5 every 28 days) compared with patients who received standard RT alone (total dose of 60 Gy). Median OS for the temozolomide and RT groups were 6 months and 4.1 months, respectively ($P$=.198).[34] Similar median OS (6.4 months) was noted in a single-arm, phase II trial of temozolomide (150–200 mg/m$^2$ on days 1–5 every 28 days) in 32 patients with GBM (>70 years with KPS ≥60).[35]

To assess this treatment strategy, 2 large, European, randomized phase III studies involving different treatment schedules of temozolomide and RT were conducted. The Neurooncology Working Group's NOA-08 trial sought to demonstrate the noninferiority of dose-intensified temozolomide alone (100 mg/m$^2$ in a 1-week-on, 1-week-off schedule) compared with standard postsurgical RT (total dose of 54–60 Gy in 30 fractions) in patients with anaplastic astrocytoma or GBM who were older than 60 and had a KPS of 60 or higher. This multicenter, phase III randomized trial failed to show noninferiority of the temozolomide regimen compared to RT alone; furthermore, patients in the temozolomide arm had a higher risk of death compared to patients in the RT arm (HR, 1.24; 95% CI, 0.94–1.63). Salvage RT in patients who did not benefit from temozolomide did not improve survival.[36]

In the other European trial, Malmstrom and associates compared 6 cycles of single-agent temozolomide (200 mg/m$^2$ on days 1–5 every 28 days), 6-week RT (total dose of 60 Gy in 30 fractions), and 2-week hypofractionated RT (total dose of 34 Gy in 10 fractions) in patients aged 60 years or older with a World Health Organization (WHO) performance status of 0–2.[37] In the intent-to-treat analysis, there was a significant disadvantage of the 60 Gy RT arm compared with the temozolomide arm (OS, 6 months vs 8.3 months, respectively). A subgroup analysis suggested an even larger benefit of temozolomide for patients 70 years or older (OS of 9 months). There was no significant difference in OS between the 2-week hypofractionated RT arm versus the temozolomide arm. Based on these findings, the authors concluded that exclusive temozolomide therapy may be an alternative to RT.[37]

Moreover, the benefit of single-agent temozolomide has been shown in elderly patients with poor performance status. In a phase II trial, 70 patients aged 70 years or older with a postoperative KPS of less than 70 were treated with temozolomide (150–200 mg/m$^2$ on days 1–5 every 28 days) until disease progression.[38] This treatment increased the median OS to 25 weeks (95% CI, 19–28 weeks), which exceeded the expected median OS of 12 weeks for a similar patient population treated with supportive care alone. MGMT promoter methylation was associated with better OS (31 weeks in patients with methylation vs 19 weeks in patients without methylation).[38] Interestingly, improved performance scores were noted in 33% of patients, enabling most of these improving patients (18 of 23) to become self-caring (KPS ≥70).[38]

## Anti-Angiogenesis in the Elderly

There is little information on the benefit and toxicity of novel agents in the treatment of elderly patients with GBM. Based on the results of phase II clinical trials that showed significant response and clinical benefit, bevacizumab (Avastin, Genentech/Roche) has been approved for the treatment of recurrent GBM.[39-41] At present, there are no data regarding the use of bevacizumab in the elderly. However, there are a number of ongoing, elderly-specific, phase II trials that will delineate the role of bevacizumab in this group of patients (NCT01149850 and NCT01443676).[42,43]

## Anti-Epileptic Medications in the Elderly

Because seizures in elderly patients can lead to serious consequences, all efforts should be made to keep these patients seizure-free.[44] Anti-epileptic agents with acceptable side effects should be chosen. Ideally, anti-epileptic drugs should have a clearance unaffected by renal impairment, not induce or inhibit hepatic enzymes, not produce neurotoxic side effects, and be available in a range of formulations.[45] The newer drugs, such as levetiracetam (Keppra, UCB) and gabapentin, are more suitable choices for elderly patients. However, more extensive clinical research on the use of anticonvulsants in this specific population is needed.[46]

## Biologic Predictors of Prognosis and Response to Therapy

Integrated genomic analyses of GBM have proposed that the main cause of the age effect is secondary to the gene expression signature of the tumor. Proneural subtype, which is associated with PDGFRA abnormalities, IDH1 and TP53 mutations, and longer survival, is more frequent in younger patients.[47,48] Patient age at the time of diagnosis loses its significance in predicting survival time when patients are stratified by gene expression subtypes and the effect of the proneural subtype is controlled. This finding suggests that the age effect in GBM is most likely due to low occurrence of the proneural subtype in older patients.[47,48] However, this matter remains controversial and requires further investigation.[49,50]

Epigenetic silencing of MGMT promoter by hypermethylation has been associated with a more favorable prognosis and response to alkylating agents, as illustrated in the EORTC 26981/22981-NCIC CE3 trial.[51] Recent studies have confirmed the predictive value of this marker in elderly GBM patients.[52-55] MGMT promoter methylation has been detected in approximately half of patients aged 70 years or older.[52-54] Patients with a methylated MGMT promoter have a much more favorable median OS than patients in the unmethylated group when treated with concurrent RT and adjuvant temozolomide.[52-55] In a recently published case series, the median OS was 15.3 months for patients with methylated GBMs versus 10.2 months for patients with unmethylated tumors ($P$=.0001). The 1- and 2-year OS rates were 74% and 28% in patients with a methylated MGMT promoter versus 32% and 7% in the unmethylated group, respectively ($P$=.001).[52]

Cytosolic isocitrate dehydrogenase 1(IDH 1) mutations have been associated with a favorable prognosis, irrespective of MGMT promoter methylation status.[49,56] In a study evaluating the prognostic effect of IDH1 mutations in GBM and anaplastic astrocytomas, IDH1 mutations were detected in only 1% of patients with GBM who were older than 60 years.[49]

Differing prognostic implications of epidermal growth factor receptor (EGFR) amplification, TP53 mutations, and CDKN2A/p16 have been reported in the elderly.[50] In this study, TP53 mutations were associated with reduced survival in patients older than 70 years (HR, 7.54; 95% CI, 2.38–23.87), whereas the opposite was true for younger patients. Furthermore, the negative prognostic effect of CDKN2A/p16 was more pronounced in patients older than 70 years (HR, 11.48; 95% CI, 1.97–66.78) than in younger patients (HR, 1.33; 95% CI, 0.66–2.67). In this series, EGFR amplification was associated with a better prognosis in patients older than 46 years.[50] However, these findings should be validated in prospective studies before firm conclusions are made.

## Conclusion

Although elderly patients with GBM generally have a dismal prognosis, age alone should not exclude them from aggressive treatment strategies or enrollment in clinical trials. In fact, there is emerging evidence that patients with good performance status may benefit from maximal cytoreductive surgery followed by concurrent RT and adjuvant temozolomide. The role of concurrent and adjuvant temozolomide chemotherapy with RT for elderly patients with GBM should be resolved by an ongoing, randomized, phase III trial by the NCIC Clinical Trials Group. Until then, combined modality treatments should be considered for otherwise healthy and fit patients with a KPS of 70 or higher. For patients with poor performance status, hypofractionated RT or single-agent temozolomide may be considered. At present, there is no available evidence for any specific second-line treatment in fit elderly patients with GBM. The role of bevacizumab in the treatment of recurrent GBM in elderly patients remains unclear, although this question is currently an area of clinical investigation. The management of elderly patients with GBM remains complex and challenging,

and advances in the care and outcome for these patients will hinge on the execution of well-designed clinical trials aimed at this distinct and increasing subpopulation.

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