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Clinical Considerations for Older Patients With Glioblastoma

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Activity Overview

Glioblastoma (GBM) is the most common primary brain tumor in the United States and occurs most frequently between the ages of 65 and 84. Treatment often consists of a combination of surgical resection, radiotherapy, and chemotherapy. Despite the frequency with which GBM occurs in patients aged 65 and older, aggressive therapies designed to maximize overall and progression-free survival are most commonly administered to patients under 65. Several studies, however, have shown that older patients can respond well to aggressive therapy and that functional status is a more important indicator of treatment outcome than age. It is important for physicians to understand that in otherwise healthy and functioning older patients, the use of aggressive therapies to treat GBM can be beneficial.

Target Audience

This activity has been designed to meet the educational needs of radiation oncologists, neuro-oncologists, and other health care professionals involved in the care and treatment of patients with brain cancer.

Learning Objectives

At the conclusion of this activity, participants should be able to:

1. Identify patient- and tumor-specific characteristics that make older patients candidates for surgery, radiotherapy, and chemotherapy
2. Recognize complications or toxicities associated with treatment in older patients
3. Formulate a treatment plan for older patients with the goal of improving disease response and quality of life

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To obtain a certificate, participants must receive a score of 70% or better on the posttest. The posttest can be accessed at the end of the activity. Please e-mail any questions to cmeinfo@curatiocme.com.

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Medium

A journal supplement was selected as the instructional format to accommodate the learning preferences of a significant portion of the target audience.

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Generic Name	Trade Name	Approved Use (if any)	Unapproved/Investigational Use
Procarbazine	Matulane	For use in combination with other anticancer drugs for the treatment of Stage III and IV Hodgkin disease; used as part of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) regimen	In combination with lomustine and vincristine for the treatment of recurrent GBM
Vincristine	Vincasar PFS	For use in acute leukemia; in combination with other oncolytic agents in Hodgkin disease, non-Hodgkin malignant lymphomas (lymphocytic, mixed-cell, histiocytic, undifferentiated, nodular, and diffuse types), rhabdomyosarcoma, neuroblastoma, and Wilms' tumor	In combination with procarbazine and lomustine for the treatment of recurrent GBM

Clinical Considerations for Older Patients With Glioblastoma

Lauren E. Abrey, MD, Thomas Finnegan, PhD, and Fabio M. Iwamoto, MD

Introduction

Glioblastoma (GBM) is the most common primary brain tumor in the United States and occurs most frequently in people aged 65 to 84 years.[1] Patients older than 65 and those older than 40 with a Karnofsky performance score (KPS) below 80 have the worst prognosis.[2] Several studies have shown that the likelihood of a GBM patient receiving surgery, radiotherapy (RT), or chemotherapy decreases with age, although other factors, such as the overall health of the patient and physician perceptions, may also influence the treatment of GBM among older adults.[3,4] When these therapies are offered to older patients (defined as those ≥65) with GBM, monotherapy consisting of surgical resection or RT is more common than chemotherapy.[4-6] Clinical studies have found, however, that older patients with GBM can benefit from combination therapy.[5] Positive prognostic indicators among older patients include good performance status (KPS >70 or World Health Organization [WHO] functional status grade I or II), younger age, and the extent of surgical resection.[5,7] The purpose of this article is to illustrate that older patients with GBM should be considered for standard therapies consisting of surgical resection, RT, and chemotherapy. The suitability for therapy should be determined on an individual basis, taking into account not only age, but additional factors such as functional status and comorbidities.

Clinical Considerations

The management of GBM in older patients can present a challenge because of differences in overall health and prognostic molecular markers compared with younger patients, as well as the potentially negative consequences associated with the use of supportive medications such as antiepileptic drugs (AEDs) and corticosteroids. The likelihood that a patient will have multiple chronic medical conditions increases with age.[8] More specifically, multiple chronic medical conditions are 7 times more likely among people aged 60–79 and 14 times more likely among people older than 80 as compared with people aged 25–39 (Figure 1).[9] A study of 1,217,103 Medicare beneficiaries (patients ages ≥65) found that 82% of the study population had at least one chronic medical condition and 65% had multiple chronic medical conditions.[10] The most common medical conditions among older people are hypertension, heart failure, vision problems, endocrine or metabolic conditions, dementia, atrial fibrillation, anemia, and musculoskeletal diseases.[10,11]

A related concern in older adults is polypharmacy. The number of patients taking multiple (≥5) medications is higher among those 65 and older than among those 18–44.[12] It is therefore important that physicians obtain information about comorbid medical conditions and any related medications before developing a treatment plan for a patient with GBM.

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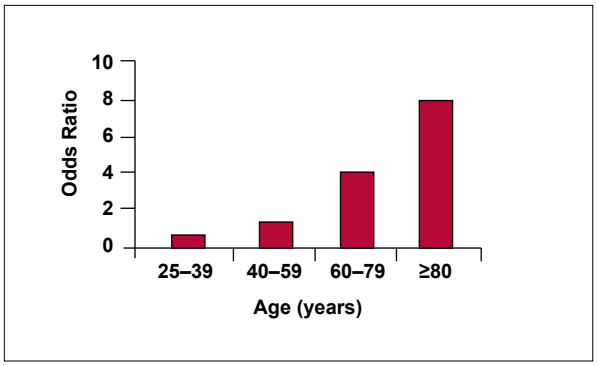

Figure 1. Risk of multiple medical conditions as a function of age.[9]

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Table 1. Differential Effects of Age on the Prognostic Significance of Molecular Genetic Markers in GBM[23-26]

	Prognostic Predictive Survival Value	
	Young Patients	**Old Patients**
TP53 mutation	↑	↓
CDKA2A/p16 deletion	↓	↓↓↓
LOH 1p	↑	↑↑↑
EGFR overexpression	↓	↑
MGMT promoter methylation	↑	↑

EGFR=epidermal growth factor receptor; GBM=glioblastoma; LOH=loss of heterozygosity; MGMT=O^6-methylguanine–DNA methyltransferase.

The Use of Supportive Medications in Older Adults

Seizures are another concern and have been estimated to occur in 40–70% of patients with brain tumors.[13,14] A common, but not recommended, practice to prevent seizure activity among patients with brain tumors is prophylactic prescription of AEDs.[15] The prophylactic use of AEDs does not prevent the occurrence of seizures in brain tumor patients with no history of seizures and is therefore not recommended.[16,17] AEDs should be used with caution in brain tumor patients, as there are multiple potentially serious interactions when AEDs are combined with chemotherapy or corticosteroids.[17] AEDs may also cause side effects that can be confused with the tumor-specific worsening of neurologic symptoms.[18] Seizure activity should be investigated in patients with a sudden change in neurologic function.

Glucocorticoids, most commonly dexamethasone, are another supportive therapy commonly administered to patients (both young and old) with brain tumors. Imaging studies have shown that glucocorticoid administration improves edema and mass effect and decreases contrast enhancement.[19] The mechanisms responsible for these changes are believed to be related to the induction of vasoconstriction and a reduction in vascular permeability.[20,21] Corticosteroids are also associated with a number of potentially serious adverse events, including hyperglycemia, increased susceptibility to infection, proximal muscle weakness, behavioral changes, low bone mass, and osteonecrosis.[22] Due to the potential adverse events, the use of glucocorticoids should be limited to patients with symptomatic mass effect or cerebral edema.

Age-related Changes in Prognostic Molecular Markers

The other factor to be considered by physicians is the prognostic difference in the molecular genetic profile of GBM tissue between younger and older patients (Table 1).[23-26] In patients older than 70, mutations in the tumor protein p53 (TP53) gene are associated with reduced survival, whereas in younger patients, these mutations are associated with increased survival.[23,24] The negative prognostic effect of the deletion of the cyclin-dependent kinase 2A (CDKA2A)/p16 gene is intensified in patients older than 70.[23,24]

Other changes to the molecular genetic profile of GBM tumor tissue confer a positive effect on survival. Loss of heterozygosity of chromosome 1p has a greater positive prognostic effect in patients older than 60 than in younger patients.[23] Overexpression of the epidermal growth factor receptor improves survival in older (≥55) GBM patients, but decreases survival in younger GBM patients.[25] Methylation of O^6-methylguanine DNA methyltransferase (MGMT) predicts a longer survival for both younger and older patients treated with alkylating chemotherapy.[26,27] Clinicians must take into account age-related changes in the prognostic value of molecular genetic aberrations when managing older patients with GBM.

Surgical Intervention in Older Patients With GBM

The surgical removal of tumor mass is often an integral part of treating patients with GBM.[28] Multiple studies

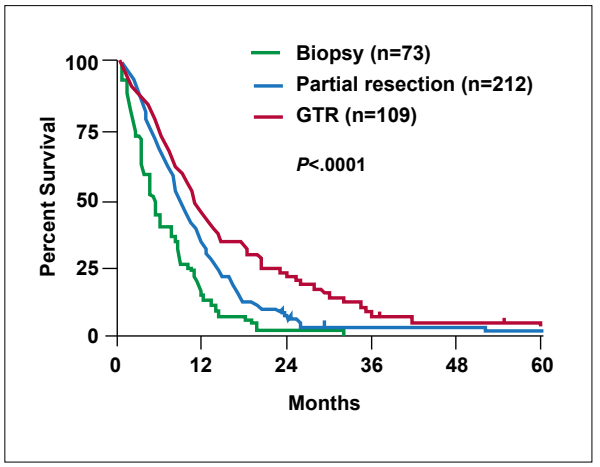

Figure 2. Kaplan-Meier curves comparing survival as a function of the extent of surgical intervention among older patients with GBM.[5]

GBM=glioblastoma; GTR=gross total resection.

have shown that aggressive debulking of tumor mass can improve presurgical KPS scores and improve quality of life.[29,30] There may be some apprehension among clinicians regarding the risk-benefit ratio of performing surgery in older patients with GBM. Evidence suggests that as patients age, they are less likely to undergo surgery and more likely to receive best supportive care.[4] Surgery may occur less frequently in older patients because of poor functional status or other health conditions that increase the risk of mortality and morbidity associated with surgery. However, among older patients who are in otherwise good health, the majority of data show that surgical intervention increases survival. As with younger patients, resection in older GBM patients has not been studied in randomized prospective trials. Most surgical studies are retrospective and have possible selection bias (eg, patients in better functional/performance status undergo resection more often than patients in poor condition).

A retrospective study of 389 patients 60 and older with GBM who were diagnosed between 1980 and 1994 showed that surgical reduction or removal of tumor mass improved survival (hazard ratio [HR], 0.39; confidence interval [CI], 0.29–0.52) and RT alone (HR, 0.52; CI, 0.37–0.73) improved survival over best supportive care (HR, 1).[4] The improvement in survival associated with surgery was similar between 275 GBM patients younger than 60 (HR, 0.49; CI, 0.31–0.77) and 389 patients 60 and older (HR, 0.39; CI, 0.29–0.52).[4]

Additional studies have shown that the extent of resection can also affect survival. A retrospective study of 128 patients 65 and older with GBM and comparable pre-operative KPS (range, 60–100) underwent either biopsy alone or surgical resection.[31] Patients who underwent a surgical resection had a median survival time of 189 days compared with a median survival time of 108 days in the biopsy-only group (P<.008).

A prospective study of 30 patients 65 and older with GBM (presurgical KPS range, 60–90) compared the survival rate of those who underwent biopsy-only with that of patients who received tumor resection.[32] Survival was improved by a factor of 2.76 in patients who received a resection versus those in the biopsy group (P=.035). There was a trend towards a significant reduction in time to deterioration in the resection group versus the biopsy-only group.

Iwamoto and colleagues published a retrospective study of 394 patients 65 and over with GBM in which the risk of death was lower in those who received a gross total resection compared with those who received a biopsy or partial resection (Figure 2).[5] A smaller retrospective study also found a survival advantage of gross total resection over subtotal resection.[33]

Further improvements have been made possible through advancements in surgical technologies, including neuronavigation, magnetic resonance imaging (MRI), and the use of 5-aminolevulinic acid (5-ALA) during surgical procedures. The effect of neuronavigation on the proportion of patients receiving a gross total resection was examined in a retrospective study of 76 adult patients with supratentorial malignant astrocytomas.[34] The results showed that 64% of patients in the neuronavigation group received a gross total resection compared with 38% of patients who received traditional microneurosurgery (Figure 3).[34]

Other technologies that build upon traditional neuronavigation techniques have also been developed to optimize outcomes. The navigation-guided fence-post procedure was designed to control for brain shift during neurosurgery and was shown to result in a greater level of tumor removal than traditional neuronavigation or traditional microneurosurgery without neuronavigation.[30]

MRI is a standard tool for the management of GBM and is typically used in the diagnosis of disease and to determine the effectiveness of treatment.[28] MRI is also used to improve the accuracy of standard neurosurgical procedures. A retrospective study of 51 patients aged 60 and older with GBM investigated the impact of combining pre-operative MRI with intra-operative navigation on survival.[35] The median survival time in patients who received both pre-operative and intra-operative MRI was 16 months; in patients who received only a pre-operative MRI, the median survival time was 11.7 months. Significantly longer survival times were

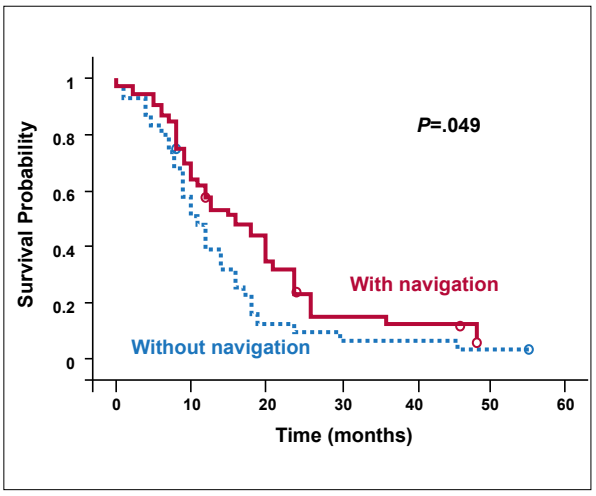

Figure 3. Kaplan-Meier curves comparing overall survival of traditional microsurgery with surgery utilizing neuronavigation in adult patients with malignant astrocytoma.[34]

Originally published in Kurimoto M et al. *Minim Invasive Neurosurg.* 2004;47:278-283. Used with permission.

seen in patients who received MRI in any capacity than in those who did not receive an MRI (no MRI vs pre-operative MRI, *P*<.0054; no MRI vs pre-operative MRI and intra-operative navigation, *P*<.0024).

In a prospective study of 38 patients with high-grade gliomas, initial total resection occurred in 37% of patients.[36] Of the remaining patients, 54% had evidence of definite residual enhancing tumor, whereas results from 10% of patients were inconclusive (considered a treatment failure in this study). When surgeons resected additional tumor tissue based on the intra-operative MRI, early postoperative MRI results indicated that 76% of patients had a total resection. The authors concluded that intra-operative MRI significantly improved the proportion of patients who received a total resection as compared with the number of total resections that would have occurred had intra-operative MRI not been used (76% vs 37%; *P*=.0004).

Another tool used to improve the extent of resection is 5-ALA. This chemical is a prodrug that results in the creation of fluorescent porphyrins that accumulate in GBM tissue and allows for the visualization (using an ultraviolet light source) of residual tumor mass throughout surgical resection.[37] A prospective study of 322 patients with malignant glioma showed that use of 5-ALA resulted in a greater number of patients receiving a gross total resection than was seen in patients who did not receive this agent (65% vs 36%; *P*=.0001).[37] More patients in the 5-ALA group achieved a 6-month progression-free survival (PFS; 41% vs 21% of patients who did not receive 5-ALA; *P*=.0003). The effect of surgery with 5-ALA on PFS was most pronounced in patients older than 55. A subsequent analysis of the 5-ALA data revealed that the extent of resection was the only valid factor that influenced survival after surgery.[38]

Brain mapping is a surgical procedure designed to maximize tumor removal and reduce the accidental resection of functional brain regions. The use of brain mapping in a prospective study of 250 consecutive patients with glioma revealed that brain regions not traditionally associated with speech were found in all patients.[39] Using a tailored approach that involved negative speech mapping (the identification of areas not involved in speech), 1.6% of patients had a persistent speech deficit 6 months after surgery.[39] The authors concluded that a tailored craniotomy with negative speech mapping allows for maximum resection and minimal adverse events for tumors located in brain regions involved in speech.[39]

In another study, 200 patients who received an awake craniotomy in combination with brain mapping for the removal of supratentorial intra-axial tumors found that 16.5% of patients experienced complications following the procedure.[40] New postoperative neurologic deficits were found in 13% of patients, although these deficits were not permanent in patients who lacked a neurologic deficit prior to surgery.

Awake craniotomy has been used as a surgical procedure for over a century. Advances in anesthesia have allowed for the incremental improvement of this technique over time. Awake craniotomy was initially performed using only local anesthesia, and over time the addition of other neuroleptic/anesthetic agents, such as fentanyl and propofol, has been adopted.[41] The adoption of propofol as a hypnotic agent used in awake craniotomy is based on the ease of titration, rapid recovery, decrease in cerebral oxygen consumption, reduction in intracranial pressure, anticonvulsant properties, and antiemetic properties.[41-43] Remifentanil can be used in place of fentanyl and may be a particularly attractive option in older patients, since its pharmacokinetics are minimally altered in older patients and in those with renal or kidney dysfunction.[41] Dexmedetomidine is a newer sedative analgesic agent and is a highly specific α_2-agonist.[41] In a study of healthy volunteers, dexmedetomidine produced sedation and analgesia that could be easily reversed by verbal or motor stimuli and was shown to result in immediate, but not retrograde, amnesia.[44] Dexmedetomidine-induced sedation is not associated with agitation or confusion and has been shown to reduce the amount of postoperative morphine required to maintain analgesia.[41,45]

Radiation Therapy in Older Patients With GBM

The use of RT to treat GBM decreases with age. A population-based study in Canada found that 78% of patients 40–49 received RT compared with 43% of patients 70–79 and 19.6% of patients 80 and older.[3] Among patients 60 and older who received RT, 36% received radiation as monotherapy, and the remainder also underwent surgery.[4] RT alone can improve survival compared with best supportive care (HR, 0.52; CI, 0.37–0.73) in patients 60 and older, although when RT follows surgery in older patients with GBM, survival improves even further (HR, 0.18; CI, 0.13–0.26) compared with best supportive care.[4] Similar results were obtained in a study of 128 patients older than 65 with malignant gliomas, in which the median survival of those who received surgery or biopsy and completed RT was 149 days compared with 50 days for patients who were either not eligible for RT or did not complete a full course (P<.0000).[31]

It is often difficult to know the general health status of patients who did not receive RT following surgery in retrospective trials. If only healthy patients received RT, it is difficult to determine whether the results speak to the health status of the patients or the impact of RT. Whittle and coworkers performed a retrospective analysis studying the impact of surgery and RT in patients older than 60 with GBM.[46] Analysis of the data revealed a significant difference between clinical health status and treatment (P<.05); patients in poor health received only a biopsy, whereas patients in better health received surgical resection combined with RT. Patients who were in better health (WHO grade 1 or 2) had longer survival times than did patients in worse health (WHO grade 3 or 4) regardless of treatment (P<.0001). The study also showed that the addition of RT significantly improved survival compared with either biopsy or surgical resection alone (P<.001), although the patients who received RT were also in better health than were patients in the other two groups.

To more accurately determine the efficacy and safety of RT in older patients with GBM, Keime-Guibert and associates performed a prospective, randomized clinical trial in which the effect of RT was examined in 85 GBM patients 70 and older who had similar KPS scores (≥70).[47] Following surgery to reduce tumor burden, patients received either supportive care or supportive care and a 50 Gy total dose of radiation. After a median follow-up of 21 weeks, the median survival of the RT group was 29.1 weeks compared with 16.9 weeks for patients who received supportive care alone (Figure 4A). The hazard ratio for death among patients who received RT was 0.47 (CI, 0.29–0.76; P<.002) compared with those in the supportive care group (HR, 1). The median PFS was 14.9 weeks with RT and 5.4 weeks with supportive care (Figure 4B). The hazard ratio for disease progression in the RT group was 0.28 (CI, 0.17–0.47; P<.001) compared with the supportive care group. Radiation-induced neurotoxicity is a concern in older patients, but this randomized study did not show significant differences between the two groups on measures of health-related quality of life or neuropsychologic function.

The total radiation an older patient receives is an important consideration when RT is used. In a study of 30 GBM patients older than 65, survival was found to depend on the total amount of radiation that followed surgical resection or biopsy.[32] In another study, GBM patients 70 and older survived significantly longer following a 5,500 cGy or greater dose of RT relative to those who received a dose of 4,000 cGy or less (P<.0001).[33]

A related controversy surrounding the use of RT in older GBM patients is whether there is a benefit to replacing the standard regimen of RT (60 Gy in 30 fractions over 6 weeks) with a shorter course.[48] The standard regimen was based on data from the Brain Tumor Study Group, which showed a survival benefit of 60 Gy compared with lower doses in patients of all ages.[49] A prospective, randomized study was undertaken to compare the effect of short-course radiation (40 Gy in 15 fractions over 3 weeks) with the effect of the standard RT regimen in 100 GBM patients 60 and older.[48] The median KPS for both groups prior to therapy was 70 and remained unchanged when assessed during the first follow-up after the initiation of RT. The overall median survival time did not differ (5.1 months for standard therapy and 5.6 months for the shorter course). Similar results were reported in a prospective and randomized trial of 44 patients older than 60 years: median survival time did not differ between patients who received 45 Gy in 15 fractions over 3 weeks and those who received the standard dose.[50]

Chemotherapeutic Approaches to Treating Older Patients With GBM

As is frequently the case with other treatment modalities, chemotherapy is often not used in older patients with GBM. In a retrospective analysis of 394 GBM patients 65 and older who were treated at Memorial Sloan-Kettering Cancer Center between 1997 and 2007, 46% did not receive adjuvant chemotherapy.[5] Other studies have shown that the use of chemotherapy decreases with age but that in more than 90% of patients who receive chemotherapy, it is administered in combination with other treatment modalities.[6,51] Several studies have shown that the use of chemotherapy in older patients with GBM has positive effects on morbidity and mortality. In addition, temozolomide, which is typically administered in

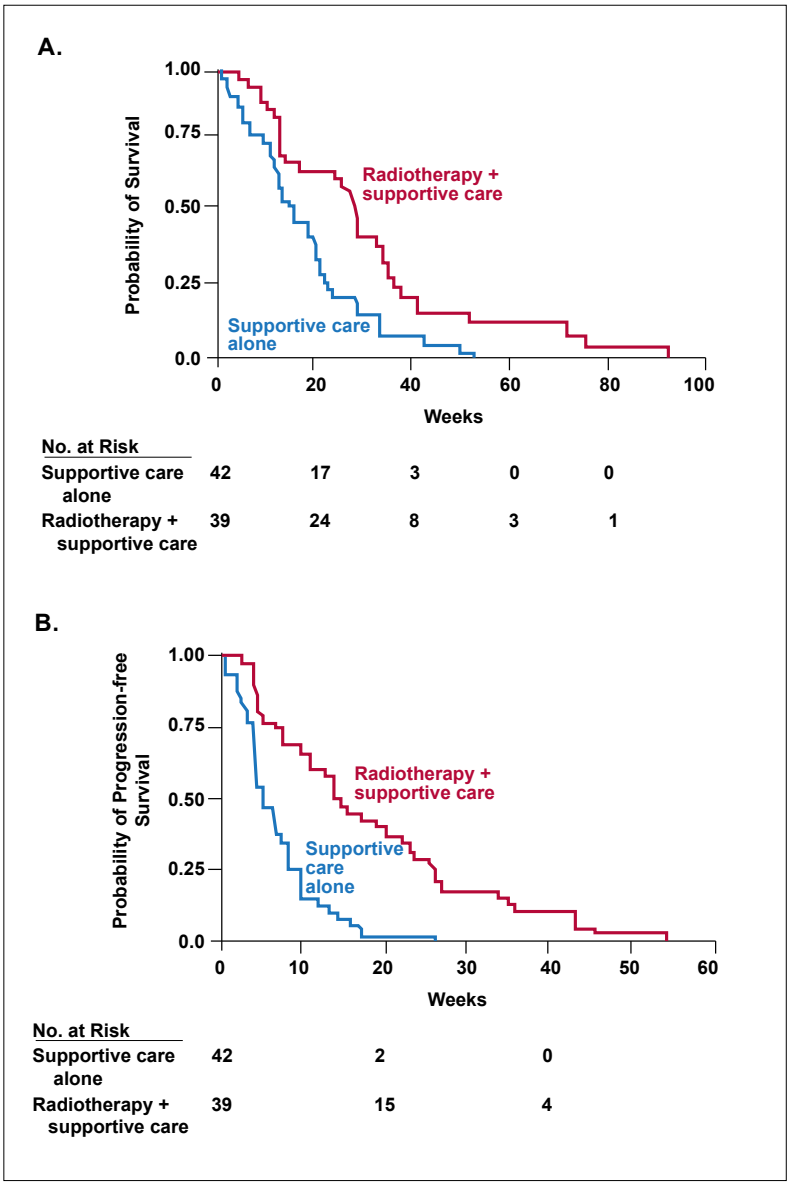

Figure 4. Kaplan-Meier curves for A) overall survival and B) progression-free survival comparing supportive care alone with supportive care and radiotherapy among older patients with glioblastoma.[47]

combination with radiation, has been investigated as monotherapy in older patients with GBM.

A prospective study in 79 GBM patients 65 and older examined the impact of chemotherapy (temozolomide or procarbazine, lomustine, and vincristine [PCV]) in patients who received surgery and RT.[52] Patients who received temozolomide had a better overall survival rate than did patients who received only surgery and RT (14.9 months vs 11.2 months; *P*=.002).[52] Survival did not differ between patients who received either temozolomide or PCV. PFS was significantly longer in the RT plus temozolomide group compared with the other groups (Figure 5). Time to progression was also longer for patients who received temozolomide relative to those receiving the other treatments (10.7 months for temozolomide vs 6.9 months for PCV vs 5.3 months for surgery and RT only; *P*<.0002). PCV was associated with a greater number of patients with grade 3–4 hematologic toxicity than was seen in those who received temozolomide. The use of temozolomide and RT in older adults is associated with an increase in grade 3–4 toxicities (including gamma-glutamyl transferase elevation, fatigue, *Pneumocystis* pneumonia, urosepsis, myelosuppression, and inappropriate antidiuretic hormone secretion) compared with patients who receive RT alone.[53]

Temozolomide is currently a standard adjuvant treatment for younger patients with GBM.[28] Several single-arm studies have examined whether the efficacy

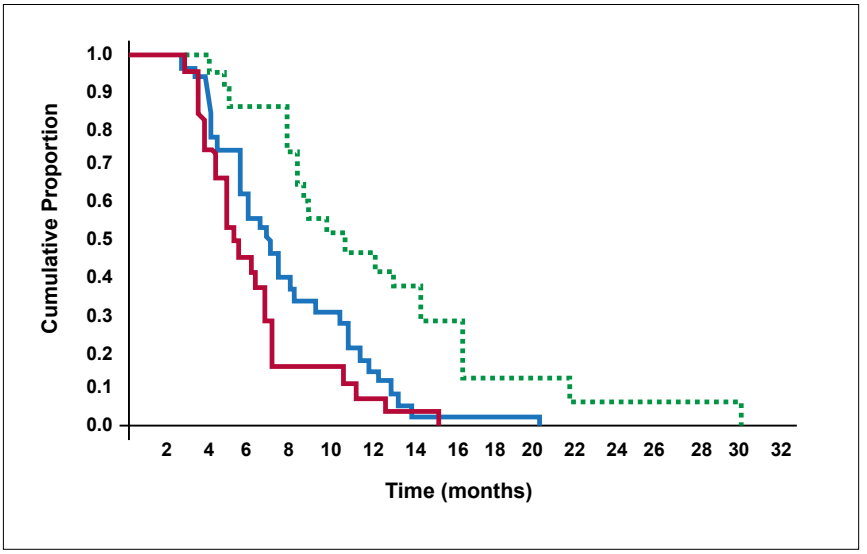

Figure 5. Kaplan-Meier curves for progression-free survival comparing radiotherapy (RT) only, RT and procarbizine, lomustine, and vincristine (PCV), and RT with temozolomide among older patients with glioblastoma. The red line indicates surgery and RT-only group, the blue line indicates surgery, RT and PCV group, and the green line indicates surgery, RT and temozolomide group.[52]

of combination therapy with temozolomide is maintained in older patients. A retrospective study of 43 GBM patients 65 and older examined the effect of combination therapy consisting of surgery, radiation, and temozolomide.[54] The presurgical KPS was 70 or higher in 60% of the patients in this study. The median overall survival, which was not affected by age, KPS, or steroid intake, was 18 months for patients who received a gross total resection, 16 months for patients who received a subtotal resection, and 6 months for those who received a biopsy. The median PFS was 4 months for all patients. Pneumonia, hematologic side effects, and rash were the most common toxicities.

A prospective study of 32 GBM patients older than 70 with a KPS of 70 or above examined the effect of surgery, RT, and concomitant and adjuvant temozolomide.[55] The median overall survival was 10.6 months, and the median PFS was 7 months. Grade 2 or higher neurotoxicity (confusion, somnolence, memory loss, dysphasia, and dizziness) during or following RT occurred in 13 patients. During concomitant temozolomide administration, two patients had grade 3 hematologic toxicity, and during adjuvant administration, seven patients had grade 3–4 hematologic toxicity.

Another prospective study examined the effect of surgery, RT, and concomitant and adjuvant temozolomide in 58 GBM patients 65 and older with a KPS of 70 and above.[26] The median survival was 13.7 months, and the median PFS was 9.5 months. Methylation status of the promoter for the MGMT gene had a significant impact on overall survival and PFS. Those with a methylated MGMT promoter did not reach a median survival, but the median PFS was 22.9 months. In contrast, patients with an unmethylated MGMT promoter had a median overall survival of 13.7 months and a PFS of 9.5 months. Both KPS and MGMT promoter methylation status were significant prognostic indicators for PFS ($P<.005$ and $P<.005$, respectively), but only MGMT promoter methylation status was a significant prognostic factor for overall survival ($P<.01$). During concomitant temozolomide administration, common mild to severe adverse events included thrombocytopenia, thrombosis, and infection. Mild to severe adverse events commonly found during adjuvant temozolomide therapy included lymphopenia, thrombocytopenia, thrombosis, constipation, nausea, infection, and changes in mental status.

Several investigators have studied the effect of replacing radiation with temozolomide monotherapy in older patients. In a pilot study of 15 GBM patients 70 and older, the use of temozolomide as the primary therapy following surgical resection resulted in a median overall survival of 6 months.[56] The authors concluded that temozolomide monotherapy may be an effective alternative to RT in older patients with GBM.

A phase II clinical trial in 32 patients older than 70 with newly diagnosed GBM found that monotherapy with temozolomide resulted in a median overall survival of 6.4 months and a PFS of 5.0 months.[57] Temozolomide led to a reduction or stabilization of the steroid dose in half of the patients, and three patients were removed from steroid therapy until disease recurrence. Grade 3–4 neutropenia occurred in 9% of patients, and grade 3–4 thrombocytopenia occurred in 6% of patients. Two patients reported grade 3–4 nonhematologic toxicities consisting of nausea, fatigue, and vomiting. In a retrospective study of patients older than 70 with malignant gliomas, overall survival did

not differ between patients who received temozolomide monotherapy and those who received radiation.[58]

The antivascular endothelial growth factor inhibitor bevacizumab may be particularly effective for GBM tumors in older patients. A retrospective study in 44 patients ranging in age from 26 to 90 years with recurrent GBM showed that bevacizumab increased overall survival (9.01 vs 6.11 months; *P*=.04) and PFS (4.25 vs 1.82 months; *P*=.01) compared with patients who received alternative therapies.[59] A further analysis of the data showed that treatment-specific differences in PFS and overall survival occurred only in patients ages 55 and older. Patients 55 and older who received bevacizumab were able to decrease or maintain a stable dose of dexamethasone for a longer period and had a longer time before experiencing functional decline compared with patients of the same age who received alternative therapies. This relationship was not seen in patients younger than 55.

Similar results were found in a study by Kreisl and coauthors that examined the effect of bevacizumab in 48 patients with recurrent GBM.[60] The overall PFS was 16 weeks, but when the data were analyzed according to age, it was found that PFS was 30 weeks for patients 53 and older and 11 weeks for those younger than 53 (*P*=.001). The most frequently reported adverse events were thromboembolism and hypertension.

Psychosocial Considerations in GBM

Based on the information provided, surgery, RT, and chemotherapy play a role in improving outcomes for older patients with GBM. However, it is important to consider the patient-specific issues that influence the use of these treatments and how physicians can overcome these issues. Multiple factors affect the quality of treatment obtained by older patients with GBM. For example, white patients were more likely to undergo surgery than African-American patients.[6] Additionally, the oldest patients, those who were unmarried, and those with multiple comorbidities were less likely to receive RT or chemotherapy in a population-based study.[6] These subpopulations seem more likely to receive suboptimal care, and social workers should be involved earlier in their management.

Several authors have suggested that communication between the physician and patient can improve overall medical care.[61] In most cases, studies on communication habits and behaviors have not focused specifically on neuro-oncology, but may instead address oncology in general or other oncology subspecialties. An important aspect of communication and decision making, especially among older adults, is patient recall. Older patients have difficulty remembering large amounts of information presented during lengthy office visits, regardless of prognosis.[62] Additional communication difficulties may be encountered in older patients who also have cognitive deficits caused by the presence of a brain tumor, and such patients may also have significant impairments in health-related quality of life.[63]

To help with the decision-making process, older cancer patients may involve caregivers. Adult children are the most common type of caregiver, followed by spouses and other relatives.[64] It is important for the physician to be aware that the patient and his or her caregiver may have differing ideas on what information relating to disease diagnosis and management is most important.[64] A challenge for physicians is therefore to determine how much information to relay to patients or caregivers. In a study of 73 colorectal cancer patients 70 and older, 44% did not want to know about their prognosis upon initial diagnosis.[65] In addition, only 25% of patients received prognostic information from their physician. Half of the patients preferred a passive role in treatment decisions, whereas the remaining patients preferred either an active or collaborative role. Of those preferring a passive role, half wanted the physician to make all treatment decisions and the remainder wanted the physician to make treatment decisions after receiving the opinion of the patient.

A preference for a passive role when deciding on treatment occurred most commonly among patients who were older, female, and less educated, and those who had a poorer performance status, more comorbidities, and newly diagnosed illness. Physicians were able to accurately assess a patient's preference for information in 44% of cases. The highest level of accuracy relating to the physician's ability to assess the informational needs was associated with patients who preferred a passive role, in which concordance was at 59%. A study of 42 radiation oncology departments in Australia and New Zealand similarly found that physicians and patients differed in what information relating to disease management was deemed important.[66] The authors concluded that physicians need to better understand the informational needs of their patients.

When approaching issues related to the treatment of patients with GBM, it is important for physicians to determine the role that the patient wants to have in his or her treatment.[61] According to Back and co-authors, there are three aspects of the treatment discussion that physicians should follow: 1) identify patient preferences for information and decision making, 2) identify all potential treatment options, and 3) describe the treatment options and confirm understanding.[61] For patients who are interested in playing an active role in the management of their disease, physicians should seek information about their

Table 2. Helpful Communication Strategies for Physicians Who Treat Cancer Patients[67]

Do	Don't	Comments
Diagnosis		
Ask patients how much they want to know	Assume that people will or will not want to know their diagnosis	Although cultural expectations may vary, most patients want to know their prognosis and options. They may underestimate their odds, too, and forego useful chemotherapy
Define "response" and "cure"		Patients can mistake a "20% chance of response" with a 20% chance of cure
Write down a list of benefits and side effects of chemotherapy	Assume that patients will know their odds of being helped	There must be some definable benefit before chemotherapy is justified (eg, "In about 60% of patients with your type of cancer, tumors will shrink by at least half with this chemotherapy")
Ask patients about their goals		Two months may be critical to one person but unimportant to another
Begin a discussion about what to do if/when the cancer is resistant to chemotherapy		This is a good place to say, "We hope to control the disease, but at some point it may grow so that it will end your life. We need to prepare for that, too."
Treatment		
The cancer is shrinking, but it is still there	Say that the cancer is responding without providing an estimate of the number of months that the response is likely to last	It is important to emphasize what is likely to happen, so that people can make plans
Be hopeful if there is reason to hope (about the cancer)		Most people can be hopeful about something, even if their cancer is growing
Begin a discussion about "DNR" orders		This is a good place to say, "The cancer is growing, and it may end your life. There are some important issues to discuss. Tell me how much you want to know."

DNR=do not resuscitate.

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values and concerns in relation to treatment values, offer a personal recommendation, and determine a timeframe for treatment decisions.[61]

Occasionally, patients may insist upon therapies that are ineffective. Factors that may contribute to the insistence of inappropriate therapies include inadequate patient-physician communication, inaccurate patient-physician perceptions, limited resources for patients, consumer-directed advertising, and late referral to hospice.[67] Methods to address these issues include talking with a colleague, determining the level of information the patient wants, honest discussion with patients regarding their prognosis, documentation of all discussions, encouraging questions from the patient, addressing symptom management, and discussing hospice early in the process of disease management.[67] Holding family conferences, providing access to research studies, and writing down options in understandable terms are all techniques that physicians can use when there are disagreements with a patient (Table 2).[67]

Clinical Trial Participation Among Older Patients With GBM

In certain instances, older patients with GBM may be candidates for clinical trials. A survey of 94 older patients with cancer indicated that 75% would be interested in participating in clinical trials.[68] The most common reasons that a patient would participate in a clinical trial were a recommendation by the patient's physician and the patient's interest in receiving an agent that will improve how he or she feels. The most common reasons that a patient declined to participate in a clinical trial were a

Table 3. Summary of Ongoing Clinical Trials for GBM That Include Older Patients

Study Title	Clinicaltrials.gov Identifier*	Age Requirement (years)	KPS Requirement	Development Phase
Delta-24-RGD for recurrent malignant gliomas	NCT00805376	≥18	≥70	I
Cediranib, temozolomide, and radiation therapy in treating patients with newly diagnosed glioblastoma	NCT00662506	≥18	≥60	I/II
Radiosurgery for glioblastoma	NCT00456612	≥66	<70	I/II
Short course of radiation for gliomas in elderly patients	NCT00386919	≥65	>70	II
Dose-intense temozolomide in recurrent glioblastoma	NCT00657267	≥18	≥60	II
Temozolomide and radiation therapy with or without bevacizumab in treating patients with newly diagnosed glioblastoma or gliosarcoma	NCT00884741	≥18	≥70	III
Radiation therapy with or without temozolomide in treating older patients with newly diagnosed glioblastoma multiforme	NCT00482677	≥65	N/A (ECOG 0-2 performance status)	III
Effect of NovoTTF-100A together with temozolomide in newly diagnosed glioblastoma multiforme (GBM)	NCT00916409	≥18	≥70	III
Radiation therapy and temozolomide in treating patients with newly diagnosed glioblastoma or gliosarcoma	NCT00304031	≥18	>60	III

ECOG=Eastern Cooperative Oncology Group; GBM=glioblastoma; KPS=Karnofsky performance scale; N/A=not applicable.

*http://clinicaltrials.gov/

recommendation by the patient's physician and concerns about the efficacy of the therapy.

Often, patients are not informed about the availability of clinical trials.[68] In addition, many clinical trials in GBM exclude patients older than 70, making it especially difficult to recommend appropriate trials to this population. Currently, there are a number of ongoing clinical trials that include GBM patients older than 70 (Table 3). It is important that future clinical trials are designed to address the management of GBM in older patients because of the current paucity of data regarding effective therapies for this patient population.

Summary

The current treatment modalities for GBM include a combination of surgical resection, RT, and chemotherapy. As patients age, they are less likely to receive aggressive forms of therapy. The disparity in treatment stems from a variety of sources. Older patients are more likely to have multiple chronic medical conditions and may be taking multiple prescription medications, both of which can adversely influence the safety of therapies for GBM. However, multiple studies have shown that older patients with GBM who are in generally good health can derive an overall survival and PFS benefit from aggressive therapy. In the development of a treatment plan for older adults with GBM, the general level of health is more predictive of treatment outcome than age.

Doctor-patient communication is an aspect of delivering optimal care that is often overlooked. Patients vary regarding how much information they want about their condition and how involved they want to be in developing a treatment plan. Data have also shown that oncology patients have an interest in clinical trial participation if it is offered by the treating physician. Despite the dearth of clinical trials that allow for the inclusion of older adults, there are clinical trials currently under way in GBM that include older patients. It is important that the clinician understands the patient's preferences. The results of future GBM studies would benefit greatly from the inclusion of older patients, because many older patients are interested in clinical trial participation, and GBM occurs most frequently in this age group.

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Clinical Considerations for Older Patients With Glioblastoma

Posttest Questions

Please select the best answer, and indicate your response on the answer sheet on the following page.

1. Which of the following is a positive prognostic factor in older GBM patients?

a. Increasing age
b. KPS ≤70
c. Maximal surgical resection
d. All of the above

2. Loss of chromosome 1p does not retain prognostic significance in older patients with malignant glioma.

a. True
b. False

3. Which of the following statements is correct?

a. All patients with GBM should be on corticosteroids to minimize edema
b. All patients with GBM should be started on anticonvulsants to prevent seizures
c. Medications for routine medical conditions will not interfere with chemotherapy
d. Polypharmacy is a serious concern in older patients and efforts to minimize medications are critical to minimizing risk of side effects and drug interactions

4. Radiotherapy has been shown to definitively improve survival in older patients with GBM.

a. True
b. False

5. Which of the following statements is correct regarding chemotherapy for older GBM patients?

a. All older GBM patients should receive adjuvant temozolomide based on the positive results of a phase III trial for patients 70 years of age and younger
b. Based on retrospective and small phase II studies, temozolomide is likely beneficial and well tolerated in a subset of older GBM with good performance status
c. Bevacizumab is contraindicated in older GBM patients because of the risk of stroke, heart attack, and intracranial hemorrhage
d. The combination of procarbazine, lomustine, and vincristine (PCV) is the most effective and well-tolerated regimen

6. Results obtained following a short course of radiotherapy over 2–3 weeks were similar to those obtained using a standard 6-week regimen.

a. True
b. False

7. Bevacizumab may be more effective in prolonging progression-free and overall survival of older patients with recurrent GBM compared with their younger counterparts.

a. True
b. False

8. What are important psychosocial factors that influence communication and the decision-making process of older GBM patients?

a. Availability of a caregiver
b. Patient's cognitive functions may be impaired by the brain tumor or underlying comorbidity
c. Patient's communication and decision-making preferences
d. All of the above

9. Which of the following statements is correct regarding clinical trials for older GBM patients?

a. Clinical trials for older GBM patients are not cost effective because of their dismal prognosis independent of treatment
b. Clinical trials for this specific population are not warranted because GBM is uncommon in older patients
c. Older patients with cancer are interested in clinical trials, and enrollment should be encouraged
d. Results of clinical trials that only included younger GBM patients can be easily used to make treatment decisions for older patients

10. In contrast to younger patients, MGMT promoter methylation has no prognostic value in older patients treated with alkylating agents such as temozolomide.

a. True
b. False

Activity Evaluation Form:

Release date: January 2010 **Expiration date:** January 31, 2011

Participants requesting credit must read the CME activity. Certificates will be issued only upon receipt of completed activity posttests, along with a completed evaluation and certificate information form.

Participants requesting CME credit can submit their posttest, evaluation, and certificate information form in any of the following ways:

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Please check one: ❒ Physician ❒ Non-Physician I claim _____ *AMA PRA Category 1 Credit*™ <up to 1.0 credits>.

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Signature _____

❒ I would like to receive information about future educational activities on the topic of glioblastoma.

(Evaluation continues on the following page.)

POSTTEST ANSWER SHEET

Please fill in your answers to the right: 1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10____

EVALUATION

1. Rate the extent to which you agree or disagree.	**Strongly Agree**				**Strongly Disagree**
• I am satisfied with the overall quality of this activity.	5	4	3	2	1
• Participation in this activity changed my knowledge/attitudes.	5	4	3	2	1
• I will make a change in my practice as a result of my participation in this activity.	5	4	3	2	1
• The activity presented scientifically rigorous, unbiased, and balanced information.	5	4	3	2	1

Please list the changes you plan on making in your practice as a result of your participation in this activity. _____

_____

If you felt the activity was biased, please explain. _____

_____

2. This activity helped me to achieve the following objectives:	**Strongly Agree**				**Strongly Disagree**
• Identify patient- and tumor-specific characteristics that make older patients candidates for surgery, radiotherapy, and chemotherapy.	5	4	3	2	1
• Recognize complications or toxicities associated with treatment in older patients.	5	4	3	2	1
• Formulate a treatment plan for older patients with the goal of improving disease response and quality of life.	5	4	3	2	1

If you felt the learning objectives were not met, please explain. _____

_____

3. What information remains unclear? _____

_____

4. Questions or comments regarding this activity _____

_____

5. How did you hear about this activity? (Please check all that apply.)

❒ Direct mailing ❒ Curatio Web site ❒ Colleague

❒ Other (Please specify.) _____

6. Time spent completing this activity

❒ <1 hr ❒ 1–1.5 hr ❒ 1.5–2 hr ❒ >2 hr

7. Suggested topics and/or speakers you would like for future programs: _____

_____

8. What is/are your preferred format(s) for earning continuing medical education credits? (Please check all that apply.)

❒ Satellite symposium ❒ Grand rounds ❒ CD-ROM ❒ Dinner meetings ❒ Internet activities ❒ Podcast

❒ Teleconference ❒ Journal supplement ❒ Newsletter/monograph

❒ Other (Please specify) _____