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Primary Brain Tumors in the Elderly

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Abstract

The incidence of primary brain tumors is highest in elderly patients, and advanced age often is a negative prognostic factor. Nevertheless, large randomized studies in this population are scarce. Elderly patients with primary brain tumors also present unique challenges, such as the presence of multiple comorbidities and polypharmacy, decreased tolerance to chemotherapy, and an increased risk for radiation-induced neurotoxicity. This review gives an overview of the treatment options for older patients with glioblastoma and other gliomas, primary central nervous system lymphomas (PCNSLs), and meningiomas. Selected elderly glioblastoma patients with good performance status may benefit from aggressive treatment with surgical resection, radiotherapy, and possibly chemotherapy. For older patients with PCNSLs, high-dose methotrexate-based chemotherapy should be the mainstay option; whole-brain radiation therapy should be avoided in chemosensitive tumors because of the high risk of irreversible and progressive neurotoxicity. Meningiomas often may be followed up in elderly patients, as they usually are asymptomatic and have a slow growth rate. Treatment for elderly patients with primary brain tumors should be individualized, and age alone should not preclude the use of more aggressive treatments.

Keywords

Elderly; Glioma; Glioblastoma; Oligodendroglioma; Astrocytoma; Primary central nervous system lymphoma; Meningioma; Primary brain tumor; Chemotherapy; Radiotherapy

Introduction

The incidence rate of both benign and malignant primary central nervous system (CNS) tumors is 18.16 per 100,000 person-years in the general population. However, the incidence for all primary CNS tumors is highest among those 75 to 84 years old (63.75 per 100,000 person-years) [1]. Moreover, as the elderly segment of the general population grows faster than any other age group, the number of primary brain tumors in older adults is expected to

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increase. Certain tumor histologies are especially common in older adults; for example, the incidence of glioblastomas, anaplastic astrocytomas, and primary CNS lymphoma (PCNSL) peaks in the seventh decade, and the incidence of meningiomas rises steadily with age [1].

Several factors influence the treatment of brain tumors in the elderly. Poor overall health status, the presence of multiple comorbidities, and polypharmacy may pose a significant challenge in managing older patients with brain tumors. In addition, advanced age is a well-known prognostic factor associated with worse survival when adjusted for histologic diagnosis and tumor grade. Moreover, elderly patients are underrepresented in clinical trials because of study-imposed restrictions, coexisting conditions, concern about the toxic effects of treatment, or the reluctance of physicians to enroll elderly patients in these trials. Consequently, no accepted standard treatments are available for most primary brain tumors in the elderly. This review gives an overview of the treatment options for older patients with glioblastoma and other gliomas, PCNSLs, and meningiomas.

Glioblastoma

Glioblastoma (grade 4 glioma) is the most common and aggressive malignant primary brain tumor. The incidence of glioblastoma increases with advancing age [2], peaking between the ages of 65 to 84 at 13.16 per 100,000 person-years in those 65 to 74 and 14.61 between those 75 to 84 years of age [1]. Glioblastomas have a poorer prognosis in the elderly than in younger patients. A population-based study showed a median survival of only 4 months among glioblastoma patients 65 years or older at diagnosis [3•], compared with 12 to 14 months in younger patients. This might be related to differences in underlying tumor biology or to characteristics of the elderly population, but the poorer survival likely is a combination of several factors [4]. For example, glioblastomas are biologically heterogeneous tumors, and small studies have shown that the influence of specific genetic alterations, such as TP53 gene mutations, allelic loss of chromosome 1p, CDKN2A/P16 homozygous deletion, and epidermal growth factor receptor (EGFR) amplification, on patient outcome is age dependent [5, 6]. For example, EGFR overexpression may be associated with improved survival in older patients, whereas the opposite is true in younger patients [5–7]. Patient characteristics also are important prognostic factors; poor performance status is a strong predictor of short survival, and comorbidities also may influence outcomes [8].

Because of the underrepresentation of elderly patients in clinical trials, optimal management of patients over 70 years of age with glioblastoma has not yet been determined. In fact, the pivotal phase 3 clinical trial demonstrating that chemoradiation with temozolomide followed by adjuvant temozolomide improved survival compared with radiotherapy alone excluded patients older than 70 years [9].

Resection Versus Biopsy

Maximal safe resection is the accepted initial step of glioblastoma therapy, as it is for other malignant gliomas. However, no large prospective randomized study comparing biopsy versus resection for gliomas is available. Although surgical resection for gliomas is widely accepted, its recommendation is based on retrospective studies showing longer survival and improved presurgical performance status, neurologic function, and quality of life. McGirt et

al. [10] reviewed 949 patients who underwent primary or secondary resection for grade 3 (26%) and 4 (74%) gliomas and observed a survival benefit with gross total and near-total resection compared with partial resection, independent of age, degree of disability, or subsequent treatment modalities. Kita et al. [11] conducted a retrospective review of 389 patients older than 60 years with glioblastoma diagnosed between 1980 and 1994 and showed that surgical resection improved survival compared with biopsy only. We also retrospectively studied 394 glioblastoma patients aged 65 or older and demonstrated that gross total resection had a survival advantage over partial resection or biopsy [8]. Finally, a small prospective study of 23 patients aged 65 and over with malignant gliomas showed that resection improved survival compared with biopsy [12]. Clinicians often are apprehensive about performing surgery in older glioblastoma patients, but with advances in surgical techniques, anesthesia, neuroimaging, and neuronavigation, older patients with good performance status and in otherwise good health may benefit from aggressive surgical intervention.

Radiotherapy

The use of radiotherapy to treat glioblastoma has been standard practice since the 1970s, when randomized studies by the Brain Tumor Study Group showed a significant survival benefit from radiotherapy compared with supportive care alone (median survival of 36 weeks vs 14 weeks) [13]. However, these studies included patients of all ages, thus the benefit of radiotherapy in older patients was still unclear. In fact, a US population-based study from 1994 to 2002 of 4,137 glioblastoma patients aged 65 and older found that 78% of those aged 65 to 69 but only 46% of those aged 80 and older received radiotherapy [3•]. Similarly, a Canadian population-based study showed lower receipt of radiation with increasing age; 78% of patients aged 40 to 49, 43% of those aged 70 to 79, and only 19.6% of those aged 80 years or older underwent radiotherapy [14]. More recently, Keime-Guibert et al. [15••] showed in a prospective randomized clinical trial that radiation therapy for glioblastoma patients older than 70 years with good performance status had a modest survival benefit over supportive care alone (median survival of 29.1 weeks vs 16.9 weeks). Importantly, this randomized study showed that no further deterioration in performance status, health-related quality of life, or neuropsychological function could be attributed to the radiotherapy itself [15••]. In this study, the investigators selected a total dose of 50 Gy to minimize the risk of neurotoxicity, which is more common in elderly patients. This dose is lower than the standard 60 Gy recommended for younger patients with malignant gliomas, and it remains controversial whether a total dose of 60 Gy would improve survival as it does in younger patients (median survival of 28 weeks with 50 Gy vs 42 weeks with 60 Gy) [16]. In fact, a prospective randomized study compared standard radiotherapy (60 Gy over 6 weeks) with short-course radiotherapy (40 Gy in 15 fractions over 3 weeks) in 100 patients aged 60 years or older with glioblastoma and found no difference in median survival (5.1 vs 5.6 months) [17]. In addition, fewer patients discontinued the short radiotherapy course (10% vs 26%), and abbreviated radiotherapy seemed better tolerated—only 23% of patients required corticosteroid increases, compared with 49% in the 6-week radiotherapy group. This study suggests that an abbreviated course of radiation may be appropriate in elderly patients, especially for those with poor performance status. Bauman et al. [18] showed an equal survival benefit from delivering 30 Gy in 10 fractions over 2 weeks to elderly patients

with Karnofsky performance status (KPS) ≤50 compared with historical controls treated more aggressively, although there was a survival advantage in treating patients with good performance status with higher-dose radiation. Minniti et al. [19] conducted a prospective trial of 43 patients ≥70 years of age with newly diagnosed glioblastoma and KPS ≥60. These patients were treated with hypofractionated radiotherapy (30 Gy in six fractions over 2 weeks) followed by adjuvant temozolomide and had a median survival of 9.3 months. In summary, these studies provide enough evidence to support the use of radiotherapy in elderly glioblastoma patients. The exact schedule and total radiation dose are still unclear, but our common practice is to offer a full 60 Gy for patients with good performance status, whereas an abbreviated radiotherapy course may be more appropriate for patients with poor performance status or significant comorbidities.

Chemotherapy

Chemotherapy is not used frequently in older glioblastoma patients, and population studies have shown that its use decreases with advanced age. Only 10% of 4137 patients over 65 years of age in a Surveillance Epidemiology and End Results (SEER) Medicare-linked database from 1994 to 2002 received chemotherapy [3•]. This is likely explained by the fact that the role of chemotherapy in elderly patients is still unclear. A meta-analysis of the data from several clinical trials before the introduction of temozolomide showed modest or no benefit in older patients [20, 21]. In addition, the landmark trial establishing the current standard of care for glioblastoma, radiation with concomitant temozolomide followed by adjuvant temozolomide, excluded patients older than 70 years [9]. However, older patients also may benefit from chemotherapy, based on retrospective or small prospective studies. A retrospective review of 394 patients with glioblastoma ≥65 years of age treated at Memorial Sloan-Kettering Cancer Center between 1997 and 2007 showed that 46% did not receive adjuvant chemotherapy [8]. Data from this study suggested that adjuvant chemotherapy given after radiation prolongs survival independent of other prognostic factors. In a prospective study of 79 patients with glioblastoma ≥65 years of age, Brandes et al. [22] indicated a clear survival advantage with maximal surgical resection and radiation followed by chemotherapy compared with surgery and radiation (overall survival, 14.9 vs 11.2 mo; P=0.002). Although there was no clear survival benefit of temozolomide over PCV (procarbazine, carmustine, and vincristine), patients who received temozolomide had a longer progression-free survival (PFS; 10.7 vs 6.9 months) and tolerated chemotherapy better. Another prospective study of 32 elderly patients aged ≥70 years with good performance status examined the effect of surgery, radiation, and concomitant and adjuvant temozolomide [23]. The median overall survival and PFS in this study were 10.6 and 7 months, respectively. Twenty-eight percent of the patients suffered from hematologic toxicity. Combs et al. [24] reported on 43 patients ≥65 years old who were treated with 60 Gy of radiotherapy and concurrent temozolomide (reduced dose of 50 mg/m^2 instead of the standard 75 mg/m^2). They reported a median survival of 11 months, and 88% of patients completed the intended therapy without interruption, suggesting that adding temozolomide to radiation may lengthen life in the elderly, with manageable toxicity. A small retrospective analysis of radiation with full-dose concurrent temozolomide (75 mg/m^2) versus radiation alone for glioblastoma patients ≥65 years of age showed that chemoradiation patients had significantly more grade 3 and 4 toxicities than patients receiving radiotherapy alone (42%

vs 0%), and the longer survival times in the chemoradiation group (8.5 vs 5.2 months) likely were secondary to patient selection (ie, extensive resection and better performance status) [25]. Few studies have examined the impact of temozolomide as an alternative to radiation in elderly patients with newly diagnosed glioblastoma and have shown a median overall survival of approximately 6 months with temozolomide alone; however, this approach should be considered experimental [26, 27]. In the United States, older glioblastoma patients with good performance status often are treated identically to their younger counterparts, receiving a 6-week course of radiation with temozolomide followed by adjuvant temozolomide. However, the evidence to support this approach is not based on more definite randomized phase 3 clinical trials. The Radiation Therapy Oncology Group (RTOG) 0525 study, a randomized phase 3 trial of standard temozolomide chemoradiation followed by either standard adjuvant temozolomide or more intense temozolomide dosing did not restrict inclusion of elderly patients and has completed accrual. This trial will provide essential prospective information on how well these regimens are tolerated in older glioblastoma patients, although it will not be able to assess the survival benefit of adding temozolomide to radiotherapy. To answer this important question, the National Cancer Institute of Canada (NCIC) Clinical Trials Group and the European Organization for the Research and Treatment of Cancer (EORTC) started a randomized phase 3 trial for glioblastoma patients aged 65 years and older comparing chemoradiation with temozolomide versus radiation alone. This trial currently is accruing, and patient participation should be encouraged.

In May 2009, the US Food and Drug Administration granted accelerated approval to bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), for recurrent glioblastoma. The approval was based on durable objective responses from two uncontrolled phase 2 trials [28, 29]. One of these trials reported that the median PFS for patients aged 53 years or older was 30 weeks, versus a median PFS of 11 weeks for younger patients. This finding was exactly the opposite of what had been reported in recurrent glioblastoma trials before the introduction of bevacizumab, when older age was associated with shorter PFS and worse outcomes [30]. A retrospective analysis of patients with recurrent glioblastoma also showed that patients ≥55 years old gained the most benefit from bevacizumab, compared with younger patients [31]. Also, older patients demonstrated a higher expression of VEGF, thereby suggesting more angiogenesis and thus more efficacy of an antiangiogenic agent in this age group. Two large randomized phase 3 trials of upfront chemoradiation with temozolomide with or without bevacizumab for newly diagnosed glioblastoma are ongoing; both allow inclusion of older patients. Participation in one these trials should be encouraged.

Anaplastic Astrocytomas

The highest incidence of anaplastic astrocytoma occurs in the elderly. Although anaplastic astrocytoma is a World Health Organization grade 3 tumor, its prognosis in the elderly is comparable with that of glioblastoma, a grade 4 tumor. A SEER–Medicare study showed a median survival of 4 months in patients ≥65 years old with anaplastic astrocytomas, which is similar to that seen in patients with glioblastoma [3•, 32]. There is no accepted standard treatment for anaplastic astrocytomas at any age, but maximal safe resection and radiotherapy are widely used. In the United States, younger patients with anaplastic

astrocytomas commonly are treated with chemoradiation with temozolomide followed by adjuvant temozolomide, similar to treatment for patients with glioblastomas. The same clinical considerations discussed earlier for elderly glioblastoma patients are useful when deciding the best approach for elderly anaplastic astrocytoma patients. The role of temozolomide in treating grade 3 anaplastic gliomas with intact 1p/19q chromosomes is being tested in a randomized phase 3 trial of chemoradiation and adjuvant temozolomide versus radiation alone through the EORTC, NCIC, RTOG, and Medical Research Council (CATNON Intergroup Trial).

Low-Grade Gliomas

Low-grade (grade 2) astrocytomas and oligodendrogliomas are more common in younger patients, and only 8% of histologically identified low-grade gliomas occur after age 60 [33]. The clinical picture, course, and prognosis of low-grade gliomas in the elderly differ substantially from those in young patients [33]. The frequency of seizures at presentation is significantly lower in older adults (age ≥60 years). Older patients have larger tumors at diagnosis, with more contrast enhancement on neuroimaging, suggesting more aggressive tumor behavior in this age group. A population-based study of patients ≥65 years of age showed that the median survival was only 9 months for patients with low-grade astrocytomas and 57 months for those with low-grade oligodendrogliomas. In general, maximal safe resection or observation alone with close follow-up is a reasonable initial option in managing low-grade gliomas in younger adults, based on a phase 3 trial that randomly assigned patients to receive early versus deferred radiotherapy until progression and demonstrated no difference in overall survival [34]. However, because of the poorer prognosis of older patients with low-grade gliomas, early radiotherapy should be considered, especially for those with incomplete resections or biopsy only, astrocytic histology, contrast-enhancing tumors, or significant neurologic symptoms.

Primary Central Nervous System Lymphoma

PCNSL, an extranodal non-Hodgkin’s lymphoma that arises from the brain, spinal cord, leptomeninges, or eyes, represents approximately 3% of all primary brain tumors. The age-adjusted incidence of PCNSL in immunocompe-tent patients in the United States has been increasing since the 1970s, and data from 1973 to 1997 from SEER registries indicate the highest rates are among the population ≥65 years of age [35]. The outcome of patients with PCNSL is influenced significantly by age and performance status. Recursive partitioning analysis of Memorial Sloan-Kettering Cancer Center data between 1983 and 2003 with an external validation set obtained from three RTOG trials identified age and performance status as the most important independent prognostic factors [36•]. In this analysis of 338 patients, those older than 50 years with KPS less than 70 had the worst prognosis, with a median survival of 1.1 years, compared with 8.5 years in patients ≤50 years of age.

Treatment of PCNSL in the elderly is associated with lower response rates and a higher incidence of both acute and delayed toxicity compared with their younger counterparts. Surgical resection has no therapeutic role in PCNSL, unlike in other brain tumors. Surgery serves a diagnostic purpose, and stereotactic biopsy is sufficient if the diagnosis cannot be

made by cerebrospinal fluid analysis or vitrectomy (in case of ocular lymphoma). Historically, patients were treated with radiotherapy alone, with reasonable tumor responses but very high recurrence rates. The median overall survival was 7.6 months in patients ≥60 years of age enrolled in a phase 2 RTOG trial examining the efficacy of whole-brain radiation therapy (WBRT) with boost to the tumor [37]. The addition of high-dose methotrexate-based chemotherapy to radiation has improved PFS and overall survival rates. In the RTOG study 93–10, patients were treated with five cycles of high-dose methotrexate (2.5 g/m^2), procarbazine, vincristine, and intraventricular methotrexate and WBRT (45 Gy), followed by high-dose cytarabine [38]. The median survival in this study was 21.8 months for patients ≥60 years of age, as opposed to 50.4 months in younger patients. However, it became clear that patients, especially older ones, treated with high-dose methotrexate and WBRT were developing significant permanent neurotoxicity, characterized by progressive leukoencephalopathy, dementia, gait ataxia, and urinary incontinence. Abrey et al. [39] treated PCNSL patients with 3.5 g/m^2 intravenous methotrexate with procarbazine, vincristine, and intra-Ommaya methotrexate, followed by 45-Gy WBRT and two cycles of high-dose cytarabine. Twenty-two older patients deferred WBRT in this study, whereas 12 older patients completed all treatment. The median survival was 33 months in the group that deferred WBRT, versus 32 months in patients who received WBRT. Late neurotoxicity was significantly higher in those who received WBRT (83% vs 6%). Patients older than 60 years who received radiation therapy rarely developed recurrent disease (8%) but frequently developed delayed neurotoxicity and died of its complications. Conversely, nearly one half of older patients (10 of 22) who deferred radiation therapy experienced tumor relapse, and most of these patients died of progressive tumor [39].

Because of the delayed neurotoxicity in older patients, deferring WBRT has been the current therapeutic strategy. The EORTC conducted a multicenter phase 2 trial in 50 patients older than 60 years (median age, 72 years) using high-dose methotrexate (1 g/m^2), lomustine, procarbazine, methylprednisolone, and intrathecal methotrexate and cytarabine [40]. The median survival was 14.3 months; cognitive function improved in 47% and was preserved in 45% of the patients until relapse, and delayed cognitive neurotoxicity developed in 8% of the patients. A retrospective cohort of 31 patients ≥70 years of age treated with high-dose methotrexate (3.5–8 g/m^2) as initial therapy showed median PFS and overall survival of 7.1 and 37 months, respectively [41]. Omuro et al. [42] treated 23 patients aged ≥60 years with temozolomide and high-dose methotrexate and reported median PFS and overall survival of 8 and 35 months, respectively. A large retrospective cohort of 174 patients aged ≥65 years treated at Memorial Sloan-Kettering Cancer Center showed a median overall survival of 25 months; 82% of the patients received a high-dose methotrexate regimen, and only 26% had WBRT as part of initial therapy [43].

Despite advances in the treatment of PCNSL and the improvement in survival noted in clinical trials and institution-based cohort studies with high-dose methotrexate regimens, population-based studies have failed to demonstrate similar outcomes. This failure may be explained by the fact that most elderly patients in the community continue to receive radiotherapy as their primary treatment. A population study obtaining data from SEER registries linked to Medicare claims from 1994 to 2002 showed that elderly patients in the community received suboptimal therapy [44]. Of 579 patients, 80% received some

treatment; of these patients, 46% received WBRT alone, 22% received chemotherapy alone, and 33% received both [44].

Meningioma

Meningiomas account for approximately 30% of all primary brain tumors and are most common in older adults [1]. The incidence rate is 21 per 100,000 person-years in the 65- to 74-year age group and increases to 35 per 100,000 person-years in adults over age 85. Most meningiomas are benign, although 5% are atypical and 2% are malignant. Most benign meningiomas have an indolent course and tend to grow very slowly. Tumor growth rate and doubling time are found to be lower in elderly patients [45, 46]. Niiro et al. [47] reviewed 40 patients ≥70 years of age and found that during an average follow-up of 41.1 (10–97) months, 65% showed no tumor growth. Although surgical resection is the definitive treatment, asymptomatic meningiomas discovered incidentally, particularly in the elderly, may be followed with serial imaging. This is especially true for patients who are poor surgical candidates [46]. The factors influencing surgical decision are age, tumor size, surgically amenable tumor location, comorbidities, neurologic deficits at presentation, and the possibility of neurologic deficits from surgery [48]. Nonsurgical options such as stereotactic radiosurgery for tumors less than 3 cm in diameter and external-beam radiation also may be considered. Patients with atypical and anaplastic meningiomas require surgery followed by radiation [49], although there are no guidelines for optimal management in elderly patients. The results of chemotherapy in meningiomas have been disappointing.

Conclusions

The incidence of primary brain tumors is highest in elderly patients, but evidence-based treatment recommendations for this population are lacking. However, there are enough studies suggesting that aggressive treatment with surgical resection, radiotherapy, and possibly chemotherapy may benefit selected elderly glioblastoma patients with good performance status. For older patients with PCNSL, high-dose methotrexate-based chemotherapy should be the mainstay treatment and WBRT should be avoided in chemosensitive tumors because of the high risk of irreversible and progressive neurotoxicity. Meningiomas often may be followed up in elderly patients, as these tumors usually are asymptomatic and have a slow growth rate. Treatment for elderly patients with primary brain tumors should be individualized, and age alone should not preclude the use of more aggressive therapies. Finally, enrollment in well-designed clinical trials should be encouraged to resolve the many current therapeutic uncertainties and eventually improve outcomes in this population.

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