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Editorial

Surgery for glioblastoma multiforme

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Malignant astrocytomas are the most common primary brain tumors, accounting for 80% of all gliomas in adults. Glioblastoma multiforme (GBM) comprises about 51% of these.[3] The incidence of GBM peaks between the 7th and 9th decades of life, making it more common in the elderly (individuals 65 years of age or older), and the incidence of GBM in this age group—the fastest growing demographic in the US—appears to be increasing.[7,8]

Unfortunately, despite the increasing relevance of GBM in elderly patients, there has been little focus on optimization of treatment in this patient population. Several studies have demonstrated that patients with GBM in this age group have a worse prognosis, and aggressive treatment is often withheld because of presumed poor prognosis, comorbidities, poor physiological reserves, and increased risks.[4,10,11,13] Barriers to clinical trial participation in the elderly population have also been documented.[14] While resection followed by radiotherapy and chemotherapy has been the overall standard of care for most patients with GBM, recent cohort and population-based studies have confirmed that elderly patients tend to be treated less aggressively, with an increase in the rate of single-modality treatment (biopsy only, surgery only, or biopsy plus radiotherapy) and surgery plus radiotherapy compared with combined-modality treatment (surgery plus radiotherapy plus chemotherapy).[1,6,12,15] However, it is apparent that selected patients who are elderly or very elderly (age 75 years or older) may indeed benefit from more aggressive treatment.[1,2,5,9,13] This paradox complicates clinical decision making and makes the development of a more systematic approach to treatment of these patients increasingly relevant.

The paper by Chaichana and colleagues[5] in this issue of the *Journal of Neurosurgery* represents an important effort toward this goal. The authors present a retrospective review of 133 patients older than 65 years of age who underwent resection of GBM at a single institution, with the goal of identifying preoperative characteristics associated with decreased overall survival. After excluding patients who underwent prior resection or treatment as well as those lost to follow-up, 129 patients (97%) with a median survival of 7.9 months were evaluable. Controlling for perioperative factors known to be associated with survival (extent of resection, radiotherapy, and chemotherapy), this group's previous retrospective, single-institution study of 520 patients of all ages suggested that age older than 60 years was associated with poor survival by multivariate analysis.[4] Similarly, the univariate analysis in the current study suggests that patient age is associated with decreased survival and, in particular, that patient age older than 75 years is associated with decreased survival compared with patient age between 66 and 75 years.[5] However, multivariate analysis revealed that age was not a significant factor in survival while preoperative Karnofsky Performance Scale (KPS) score less than 80, increasing tumor size, chronic obstructive pulmonary disease (COPD), and the presence of motor, language, or cognitive deficits were associated with decreased survival in this patient population as in the previous report. The authors describe a classification scheme based on the number of these negative prognostic variables exhibited by each patient and demonstrate that this approach yields 3 classes of patients with statistically different median survival times of 9.2, 5.5, and 4.4 months, which the authors propose might be useful in making decisions regarding resection in these patients.

These findings contribute to a more nuanced understanding of the relevance and importance of age in the treatment of elderly patients with GBMs. Age does appear to be associated with decreased survival as suggested by previous studies,[4,10,11,13] and in particular, age older than 75 years appears to be associated with decreased survival in comparison with patients between 66 and 75 years of age. However, the influence of age appears to be relative rather than absolute. Consistent with earlier studies, preoperative motor, language, and cognitive deficits, as well as a KPS score less than 80 and a tumor diameter larger than 4 cm, appear to have a much greater association with decreased survival than absolute age in these patients, increasing the risk of death by approximately 3.5-, 2.3-, 1.8-, 1.8-, and 2-fold, respectively.[4,5] Surprisingly, the only comorbidity that appeared to exert a significant adverse influence on survival was COPD. Thus, in the proposed 3-tiered model, elderly patients with none or one of the above factors noted as negative prognostic features would still be expected to have a median survival time consistent with the elderly population as a whole regardless of age (9.2 months), while those with 2 or 3 of the features would fall into the second group (5.5 months), and those with 4 or more characteristics would be expected to have further diminished survival (4.4 months).

As the authors acknowledge, single-institution retrospective studies such as this one require validation in an independent data set or a prospectively followed cohort. Additional limitations include a lack of data on molecular markers of the tumors or the social support network available to the patients, which may be associated with

survival.[1,16] Recent studies have suggested that quality of life and quality of health are also important considerations in determining treatment approaches in the elderly, and that the variables associated with these qualities appear to vary with patient age.[16]

As the population of patients 65 years and older continues to increase, clinicians will be faced with an increased incidence of GBMs in the elderly. Many of these patients will likely consider treatment despite the poor chance for cure. Optimization of clinical management of GBM in the elderly is currently controversial and poorly understood, making the treatment in this population clinically challenging. However, the study by Chaichana and colleagues provides a framework on which we can begin to consider the options in a more rational and systematic fashion.

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Response

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We greatly appreciate Dr. Sloan's insightful and thoughtful comments. We agree that despite the increasing relevance of GBM in older patients (age > 65 years), there has been little focus on optimizing treatment for this patient population. There are a growing number of studies showing that aggressive therapies are often withheld within this population because of presumed poor prognosis, comorbidities, poor physiological reserves, and increased risks.

The goal of our study was to highlight the fact that some older patients may actually benefit from aggressive intervention typically limited to younger patients. We found that the preoperative factors that were independently associated with decreased survival were KPS score less than 80, COPD, motor deficit, language deficit, cognitive deficit, and tumor size greater than 4 cm. These factors can be used to identify 3 distinct groups with disparate survival times. Patients with 0–1 of these factors had a median survival of 9.2 months, while patients with 2–3 and 4–6 factors had median survival times of 5.5 and 4.4 months, respectively. This classification scheme can be used to identify which older patients may most benefit from aggressive surgery. Interestingly, age is not used to identify which patients have better or worse prognosis among these older patients. As Dr. Sloan stated, age is relative.

While we believe our study offers useful insights into optimizing the care for older patients with GBM, we realize our study has limitations. This study is retrospective and limited to patients who underwent nonbiopsy resection, and we did not evaluate tumor genomics or molecular markers. However, we believe that this study can be used as a framework for future studies. These future studies in older patients with GBM include prospective studies evaluating the role of our classification scheme in determining prognosis, identifying patients who may most benefit from adjuvant therapy, and identifying older patients who are more ideal surgical candidates.

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