Nothing Ventured, Nothing Gained: Treatment of Glioblastoma Multiforme in the Elderly

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In this issue of the *Journal of Clinical Oncology*, Roa et al.1 present results of a prospective randomized clinical trial of patients ≥ 60 years of age with glioblastoma multiforme (GBM), the most common and lethal of all primary brain tumors in adults. Patients either received a standard course of radiation therapy (RT), 60 Gy in 30 fractions over 6 weeks, or short-course RT, 40 Gy in 15 fractions over 3 weeks, without chemotherapy. The primary end point of the trial was overall survival. Of the 100 patients randomly assigned, 95 were eligible and analyzable. The median survival times and 1-year survival rates were similar between the two regimens; 5.1 months and 9% for standard RT, and 5.6 months and 15% for short-course RT, respectively. All patients had died by 2 years. On the surface, the authors’ conclusion that “the abbreviated course of RT appears to be a reasonable treatment option for older patients with GBM” seems quite reasonable. However, the data require closer scrutiny, and the conclusion needs several qualifications, before all elderly patients with GBM are treated with short-course RT alone.

A number of prognostic factors play an important role in determining the survival of patients with GBM. In a recent re-analysis of the original Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis database, of 1,672 GBM patients, the most important prognostic factors were age, Karnofsky Performance Status (KPS), extent of surgical resection, and neurologic function.2 Age had the greatest impact on survival, with “older” defined as ≥ 50 years of age. Older GBM patients were divided into two groups. The more favorable group had KPS ≥ 70, gross or subtotal resection, and better neurologic function; their median survival time and 1-year survival rates were 11.2 months and 46%, respectively. The less favorable group had either KPS < 70, biopsy alone, or poor neurologic function; their median survival time and 1-year survival rates were 7.5 months and 28%, respectively. Both RTOG groups of older GBM patients had better median survival times and 1-year survival rates than either the standard or short-course treatment arms of the Roa et al1 study. Why did these patients fare so poorly? First, they were a prognostically unfavorable group from the start, with a low median KPS of only 70 in both treatment arms. Second, biopsy alone was performed in 39% of patients, with only 9% of patients undergoing gross total resection, compared to biopsy in 17% and gross total resection in 19% of 645 patients treated on three consecutive RTOG clinical trials.3 In that study, the median survival time was 6.6 months with biopsy alone, compared to 11.3 months with resection. A similar observation was recently made by the Glioma Outcomes Project in a group of 565 patients with malignant glioma (primarily GBM) diagnosed between 1997 and 2001.4 The value of debulking GBM in the elderly has also now been shown in a small Finnish randomized clinical trial recently reported by Vou-rinen et al.5 In that study, 23 patients > 65 years old with malignant glioma (83% with GBM) were randomly assigned to biopsy only or to surgical resection, followed by RT. The median survival time of 5.6 months was significantly longer with resection, compared to 2.8 months with biopsy. When compared to biopsy, resection is also associated with improved quality-of-life in older GBM patients.6 Third, patients in the Roa et al1 study were not allowed to have chemotherapy until recurrence. Although the benefit of up-front chemotherapy for malignant glioma is modest, a meta-analysis of 3,004 patients treated on 12 controlled clinical trials of postoperative RT in which patients were randomly assigned to RT, with or without chemotherapy, showed a 6% increase in the 1-year survival rate (from 40% to 46%) with chemotherapy, and a 15% relative decrease in the risk of death—differences which were significant, irrespective of histology, age, performance status, or extent of surgical resection.7 The value of combined RT and chemotherapy in the elderly with GBM has now been shown in a
small Italian randomized clinical trial, recently reported by Brandes et al. Seventy-nine patients > 65 years old received RT alone, RT plus procarbazine-lomustine-vincristine chemotherapy (median of two cycles per patient), or RT plus temozolomide chemotherapy (median of five cycles per patient). The median survival time and 1-year survival rates were 11.2 months and 32% with RT alone, 12.7 months and 56% with RT + procarbazine-lomustine-vincristine, and 14.9 months and 73% with RT + temozolomide. Survival was significantly better with RT + temozolomide compared to RT alone. KPS > 70 was also associated with significantly better survival.

Taking this additional information into account, an expanded conclusion of the Roa et al study presented in this issue of the Journal of Clinical Oncology might include the following: patients with GBM who are probably the most appropriate candidates for short-course RT alone include those who are older (ie, ≥ 50 years of age), have a KPS of ≤ 70, poor neurologic function (ie, unable to work based on the original RTOG definition), and who are only able to undergo biopsy of their tumor. Such patients would have not been eligible for the randomized trials included in the Medical Research Council malignant glioma meta-analysis; therefore, the value of chemotherapy is unknown (but probably minimal) in this setting. All other older patients, such as those with KPS ≥ 70-80, better neurologic function, and who undergo subtotal or gross total resection (which should be attempted whenever feasible) should be treated with a more aggressive approach, including standard RT (60 Gy in 30 fractions over 6 weeks or the equivalent) and temozolomide chemotherapy (although an optimal chemotherapy regimen has yet to be defined), with an expected median survival time in the range of 7.5 to 14.5 months, depending on other prognostic factors. In addition, prognostically favorable older GBM patients should be included in prospective therapeutic combined-modality clinical trials. Lastly, quality-of-life issues must also be considered in the older GBM patient, including the acute and chronic sequelae of RT, chemotherapy and steroids, the impact of comorbid disease, and both performance status and neurocognitive function in long-term survivors.

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The author indicated no potential conflicts of interest.

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