Examining the role of radiosurgery in treatment of glioblastomas

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Glioblastoma continues to be a devastating illness with more than 10,000 new cases in the United States each year. Despite advances in image-guided surgery, chemotherapeutic options, and recently the usage of bevacizumab, the median survival of glioblastoma has not changed significantly. More recently, however, we have seen improvement in the percentage of patients who are living at two and five years.

The standard management of glioblastoma consists of surgical resection when feasible, especially for tumors located in lobar brain regions, followed by conventional fractionated external-beam radiation therapy. Most patients enter treatment using the STU PP regimen which adds temozolomide chemotherapy during the radiation therapy treatment component and then increases the dose of temozolomide after completion.

Over the years, radiation therapy has proved to be the treatment standard which must be applied to all patients to increase the response rate and improve median survival. Our approach has been to try to maximize the benefit of radiation modalities by using radiosurgery as an adjuvant in the treatment of glioblastoma during multimodality treatment of glioblastoma patients.

We have recently completed a retrospective outcome analysis of 297 patients who underwent Gamma Knife radiosurgery as part of the treatment regimen between 1988 and 2007. Two-thirds of our patients also had concomitant temozolomide, and all patients received postoperative conformal, fractionated external-beam radiation therapy (median dose of 60 Gy in 2 Gy fractions).

Gamma Knife radiosurgery was performed using precise head-frame guidance coupled with intraoperative MRI scan to identify the target volume. Gross tumor volume was defined as the paramagnetic contrast enhancing tumor edge. Patients received boost radiosurgery (median dose) to the tumor margin of 15 Gy.

Outcome measures included overall survival from the initial diagnosis, overall survival after radiosurgery, and progression free survival. In this series of patients, the median survival time from diagnosis was 17.7 months (95%, CI 16.4-19.0 months). Factors associated with improved overall survival were younger age, smaller tumor volume, and the prior use of chemotherapy. The median survival time after radiosurgery was 8.9 months. Patients whose tumor volumes were 14 cc or larger were compared to patients whose tumors were smaller (less than 14 cc) (see table above). The one-year, two-year, and five-year survivals after radiosurgery in patients with tumor volumes less than 14 cc were 47.8%, 11.6%, and 8.1%. Patients with larger tumor volumes had one-year survivals of 27.7%, 9.4%, and 0.9%. No patient suffered acute morbidity or early toxicity from adding radiosurgery. Adverse radiation effects, if detected, were noted at an average of 1.7 months in 20% of patients. The procedure was well tolerated by all patients otherwise.

Glioblastoma remains a challenging clinical disorder. The addition of a multimodality treatment option that includes radiosurgery (and followed by the additional use of bevacizumab), will hopefully continue to improve median survivals as well as increase the percentage of patients who survive one to five years or more.

Early introduction of radiosurgery in conjunction with bevacizumab may be a potent combination treatment for eligible patients. Bevacizumab may improve the radiobiological response of radiosurgery and at the same time reduce the detection of adverse radiation effects.

In conjunction with industry and multiple participating centers of the North American Gamma Knife Consortium, we anticipate a clinical trial using radiosurgery with bevacizumab. We plan to expand the target volume to include the contrast-enhancing volume plus a 1 cm “border zone.” It is this “border zone” adjacent to the contrast-enhancing tumor mass that represents the area of delayed progression and clinical recurrence in most patients. •

Childhood glioma study (continued from back page)

These studies take advantage of unique institutional resources provided by the University of Pittsburgh Cancer Institute Immunological Monitoring and Cellular Products Laboratory, which evaluate various parameters of immune response in children treated on this study.

Patients from age 18-months to 21 are currently being recruited for five distinct strata: 1) newly diagnosed brainstem gliomas treated with irradiation; 2) newly diagnosed non-brainstem malignant gliomas treated with irradiation; 3) newly diagnosed malignant gliomas in patients who have received chemo-irradiation therapy; 4) recurrent malignant gliomas; 5) progressive recurrent low-grade gliomas.

To date, 28 children have been treated, and although the results are preliminary, three children have had objective evidence of tumor regression on MRI and all but four of the others have had disease stabilization through at least two vaccine cycles, in many cases substantially longer. Eleven of 13 patients who have undergone immunological evaluation have shown at least some response to the vaccine antigens. •