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Editorial

Multiple craniotomies

Atom Sarkar, M.D., Ph.D., and E. Antonio Chiocca, M.D., Ph.D.

Ohio State University Medical Center, Columbus, Ohio

The submission, "Multiple craniotomies in the management of multifocal and multicentric glioblastoma" by Dr. Hassaneen and colleagues from The University of Texas M. D. Anderson Cancer Center[4] represents a unique contribution to the neurosurgical literature. To appreciate the authors' accomplishment, based on 2007–2008 Central Brain Tumor Registry of the United States report, an organization that gathers epidemiological data on primary brain tumors, 73,583 CNS neoplasms were tabulated.[2] Of that number, just a little over 20,000 lesions represented gliomas. Hence, the frequency of glioblastomas seen at any one institution is necessarily limited. Even less frequent is the appearance of 2 lesions—regardless of whether they are classified as multicentric or multifocal glioblastomas. As such, it is no wonder that it took the M. D. Anderson Cancer Center group 15 years to collect sufficient clinical data for their study.

Nearly 60 years ago, a grading scale was devised by the pathologist Kernohan[5] that linked tumor grade to survival—with survival then being only 6 months. Improvements in microneurosurgical techniques, neuroanesthesia, neuroimaging, chemotherapy, and radiotherapy have somewhat improved the outcomes in patients with aggressively managed tumors (surgery/chemotherapy/radiotherapy). In fact, median survival in a patient with optimal care for a glioblastoma is now almost 15 months,[11] an achievement that still needs considerable improvement. Intuitively, in the rare case of a patient harboring 2 high-grade lesions one would presume the patient's survival would be shorter. It is this very patient population and this presumption that Hassaneen and colleagues[4] address.

From the M. D. Anderson Cancer Center's clinical registry the authors retrospectively obtained data on 20 patients with either multicentric or multifocal glioblastomas, in whom multiple craniotomies were performed during a single session between 1993 and 2008. These patients were compared to 20 control patients in whom a craniotomy was made to excise a solitary glioblastoma. The groups were matched with respect to age, year of surgery, tumor functional grade, extent of resection, and Karnofsky Performance Scale score. The authors found that aggressive resections led to median survival times of 9.7 months in the multifocal/multicentric glioblastoma (study) group and 10.5 months in the solitary glioblastoma (control) group. Surgical complications and mortality rates were not statistically different between the study and control groups. This prompts the authors to conclude that aggressive "100%" resection of all enhancing glioblastomas is warranted to optimize patient outcomes, even using multiple craniotomies.

There are increasing data as well as belief that extent of tumor resection in both high-grade and low-grade gliomas leads to better outcomes based on retrospective data,[1,3,8,9] and now there is prospectively accumulated data showing that the extent of resection does lead to increased survival.[6,10] However, a Cochrane Database of Systematic Reviews for "Biopsy versus resection of high grade glioma" concludes that, due to a lack of randomized control trials, what most physicians still take at face value, biopsy is less risky than open surgery, but will not improve symptoms or extend survival, whereas craniotomy can relieve symptoms, but there is uncertainty whether it extends survival.[7] Thus, Hassaneen and colleagues[4] question common wisdom and provocatively escalate the debate on the role of surgical treatment for this unfortunate patient population. The reader should be aware that one limitation of the current analysis is that there is no comparison to a group of patients with multifocal or multicentric disease treated by biopsy or subtotal resection alone.

Interestingly, the results from this study do seem to suggest that outcome is worse in patients who present with newly diagnosed multifocal disease. By definition, the multifocal lesions were represented as contiguous areas of T2-weighted signal on MR imaging, whereas multicentric lesions were not. Therefore, the multifocal glioblastomas may represent a widely invasive mass, whereas the multicentric glioblastomas may represent distinct tumor foci arising synchronously in the brain. In a subgroup analysis of patients with newly diagnosed lesion only, median survival was 9.6 and 12.9 months, respectively, in patients with multifocal glioblastomas and multicentric glioblastomas. The median survival in patients with a single glioblastoma was 14.6 months. Therefore,

the patient with multifocal disease did fare worse and even for the patient with multicentric disease there may be a trend for worse survivorship, in spite of the aggressiveness of resection.

The M. D. Anderson Cancer Center group should be congratulated for the comparable results achieved in such an inordinately challenging clinical population, multiple glioblastomas, compared with the "routinely" challenging solitary glioblastoma population. Deficiencies such as lack of randomization in a prospective manner, variations in postoperative treatment protocols, and limited statistical population are fair yet effectively moot given the paucity of patients and the time required to gather even this limited number of patients to the study.

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Response

WAEL HASSANEEN, M.D., DIMA SUKI, PH.D., AND RAYMOND SAWAYA, M.D.

The University of Texas M. D. Anderson Cancer Center, Houston, Texas

We appreciate the comments of Drs. Sarkar and Chiocca regarding how aggressively the patient with multifocal and multicentric glioblastoma should be treated. Although we could not supply a firm answer to that question, our study gave us a glimpse of a challenge to the common conservative wisdom adopted for many years in the management of these patients.

The main objective of our study was to compare the postoperative morbidity rates in patients undergoing either single or multiple craniotomies in the same surgical session for the resection of multifocal or multicentric glioblastomas. We found no significant morbidity differences between the 2 groups with respect to number of craniotomies received.

Our results also showed that patients with newly diagnosed multifocal glioblastomas had a worse outcome. We agree with Drs. Sarkar and Chiocca that multifocal disease represents a widely invasive pathological entity. Therefore, we suggest that the pathogenesis and behavior of multifocal glioblastomas differ from these characteristics in the multicentric form, and we should not group them as one entity.

Indeed, we agree that the absence of a comparative group of patients with multifocal or multicentric disease treated by biopsy or subtotal resection alone represents a limitation in our study. We identified 10 cases treated surgically between June 1993 and July 2008 in which the patients had multiple glioblastomas and in which only 1 tumor was resected. The median survival time of these 10 patients was only 5.7 months compared with 9.7 months in our cohort having multifocal/multicentric lesions, which is consistent with our conclusion that removal of all glioblastoma foci is necessary to prolong survival; however, this difference was not significant ($p = 0.30$). Moreover, these patients could not be matched according to the same variables that were used for the 2 larger cohorts. Thus, we did not wish to include this information in our paper.

Finally, we believe that conducting a multiinstitutional prospective study is the way to answer the question as to how aggressively the patient with multifocal and multicentric glioblastomas should be treated.

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