Editorial

Brainstem gliomas

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Brainstem gliomas are a heterogeneous group of tumors that include biologically low-grade lesions, such as dorsally exophytic brainstem gliomas, which are often pilocytic astrocytomas histologically, and extremely malignant lesions, such as diffuse intrinsic pontine gliomas (DIPGs) of childhood, which are nonpilocytic astrocytomas of Grade II or higher. Studies in the 1980s and 1990s called attention to the drastically different growth characteristics and prognoses of these lesions.³ For children with DIPGs who exhibited characteristic imaging features on MRI in the context of a typical clinical syndrome of rapidly progressive cranial neuropathies and long-tract signs, the survival results using a host of treatment regimens during this era were so consistent and so poor that biopsy was thought to add little other than risk to treatment planning.^{1,4,7} Accordingly, biopsy for typical DIPGs was largely abandoned in many centers in the 1990s, and the procedure was eliminated as an entry requirement from most cooperative group treatment protocols.

This paradigm shift had the unintended consequence of limiting access to tumor specimens that might yield new insights into tumor biology and fostered a long-standing controversy among physicians caring for children with DIPGs about the role, or lack thereof, for biopsy. Notwithstanding this perspective, biopsy of brainstem gliomas did not cease entirely. Atypical pediatric lesions or tumors in adults for which the aforementioned natural history was less certain still regularly underwent biopsy procedures. Given that the criteria for defining a DIPG in children as “atypical” and for considering biopsy vary widely among pediatric neurosurgeons, as highlighted both by a recent survey⁶ and a consensus conference at the National Institutes of Health, it is clear that a sizable and possibly increasing percentage of such tumors are undergoing biopsy. In some institutions, particularly in Europe, biopsy procedures for otherwise typical DIPGs

have also been performed in an effort to glean insights that might guide selective implementation of molecularly targeted therapy, to obtain biological material that might lead to future improvements in therapy, or to conclusively establish a diagnosis with direct tissue confirmation.^{8,9} The recent observation of characteristic molecular features in subsets of DIPGs in children has reinforced interest in considering biopsy as a way to guide tailored treatment approaches based on molecularly stratified treatment protocols.^{5,10} An important consideration in planning such studies is the safety and diagnostic yield of brainstem biopsies.

In that context, the observations of Dellaretti et al.² are of interest from several perspectives. The authors reviewed their institutional series of 142 patients who underwent stereotactic biopsy of brainstem lesions. Complication rates were not insignificant, with 1 death and 13 “definitive” complications among the 142 patients, and 9 cases with “negative,” presumably nondiagnostic, biopsies. Among the cases that were diagnostic, 10 were “nonneoplastic” and 23 were tumors other than diffuse brainstem gliomas. The 100 remaining patients, who were the main focus of the study, included 37 children and 63 adults. Postbiopsy treatment was heterogeneous, with 84 patients receiving focal irradiation, 7 others dying before the initiation of treatment, and 9 not receiving treatment. Chemotherapy, if used, was mainly administered at the time of disease progression. The authors noted a substantially greater survival in patients with diffuse low-grade gliomas than in those with diffuse high-grade gliomas. They also noted that survival was significantly longer in patients with nonenhancing tumors than in those with enhancing lesions. Although they did not detect survival differences between children and adults, the median survivals differed substantially (16 and 25 months, respectively). Multivariate analysis indicated that only histological grade was significantly associated with prognosis. It is not clear to what extent location or imaging characteristics, apart from enhancement, were considered in the multivariate model, which would have been of interest in view of the adverse association between pontine location, in particular DIPG versus other growth patterns, and outcome in children with brainstem gliomas.

Although this study is of interest because of the sheer

number of brainstem tumors that underwent biopsy and the frank accounting of the incidence of complications, the analysis would have been strengthened by further examination of the imaging characteristics and mode of presentation of the diffuse brainstem gliomas, to define which tumors had typical imaging features of DIPGs and a characteristic natural history and which tumors did not. The enhancing tumors, accounting for more than half of the series, may have been considered atypical by many investigators, since the majority of pediatric DIPGs show little enhancement at diagnosis or focal enhancement within a much more extensive area of T2 and FLAIR signal abnormality. In contrast, pediatric brainstem gliomas that exhibit focal enhancement that largely follows the distribution of T2 and FLAIR signal change may be lower-grade lesions, and, as the authors observed, patients whose tumors had low-grade histology had a better prognosis. It is difficult to determine how many of the tumors were typical-appearing DIPGs with T2 or FLAIR signal change extending from the ventral to the dorsal surface of the pons, and whether enhancement had an association with outcome when taking this factor into account. Because observations from childhood malignant gliomas cannot be generalized to adults, it is less clear that a typical DIPG imaging phenotype carries the same natural history in adults as in children, but this sort of analysis would have been of interest.

Thus, it is difficult in this series to extricate the issues of imaging typicality, tumor location, presenting symptoms, age, histology, and enhancement, since these features may have age-related associations that differ between children and adults. Expanding this analysis to include these additional features would substantially strengthen the prognostic conclusions that can be drawn from this sizable clinical experience. The authors' sample set would also provide a unique opportunity to examine molecular correlates of the prognostic differences observed, and whether there are differences in molecular features between gliomas in adults and children, which may help to further guide treatment planning. (<http://thejns.org/doi/abs/10.3171/2012.3.JNS12590>)

Disclosure

The author reports no conflict of interest.

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Response

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We thank Dr. Pollack for his comments concerning a very controversial issue involving brainstem gliomas.

The current prognosis for diffuse intrinsic brainstem glioma remains dismal, despite more than 3 decades of clinical research. Few studies have been conducted regarding prognosis and prognostic factors in brainstem gliomas.^{3,4} This may be due to the low incidence of these tumors and the fact that histopathological diagnosis is rarely confirmed.

The use of stereotactic biopsy in the diagnosis of brainstem tumors has become less popular; this is particularly true following the publication of the studies by Epstein¹ and Epstein and McCleary.² The authors published 2 papers in consecutive years condemning the biopsy of these tumors. In 1985, Epstein¹ stated that a small biopsy specimen does not appear to provide useful information. Epstein and McCleary² followed this a year later with the comment that no consistent useful information could be obtained from biopsy samples.⁴

However, the present study demonstrated that a biopsy sampling is a safe procedure and can provide useful information regarding patient diagnoses and prognoses.

We obtained a diagnosis rate of 93.7%. Regarding complications in the current series, 1 procedure-related death occurred, and 13 patients (9.8%) presented with definitive complications.

Of greater significance, the study series revealed that, of the 3 factors investigated, univariate analysis determined that contrast enhancement and histological grade were significant prognostic factors but that age was not; however, in multivariate analysis, only histological grade remained a significant prognostic factor.

It is highly probable that conventional fractionated radiotherapy will not remain the only efficient treatment for diffuse brainstem glioma over the next few decades. In addition, for patients with low-grade gliomas, an initial observational policy is being adopted, followed by treatment when the disease progresses clinically.^{5,6}

We fully agree that further studies are required to elucidate this controversial issue, particularly studies involving molecular markers, to assess whether they have similar importance to that demonstrated in supratentorial gliomas.

Moreover, new chemotherapy, gene therapy, or immunotherapy, alone or in combination, will almost certainly succeed in improving the outcomes in these patients, and these therapies will undoubtedly require tissue sampling for diagnostic confirmation and histological grading, for molecular marker studies, or for immunological purposes prior to adopting target therapies.⁶

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