Biopsy for diffuse intrinsic pontine glioma: a reappraisal

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DIFFUSE intrinsic pontine gliomas (DIPGs) are regionally specific gliomas that arise in a relatively narrow age range in children. As opposed to a pontine location, tumors that arise in the medulla or midbrain are often WHO Grade I or II tumors and have a markedly different prognosis than DIPGs. The characteristic location as well as the presence of extensive infiltration in the ventral pons means that resection is not possible. The overall lack of treatment options, and the resulting dismal prognosis associated with a diagnosis of DIPG has historically led to a sense of nihilism among treating physicians. The biological behavior of these tumors has long been thought to best fit with adult WHO Grade IV astrocytoma, and it was also assumed that the molecular features would be similar to those observed in other locations in the brain. These assumptions led to the use of many experimental agents that are used in the context of adult clinical trials for WHO Grade IV astrocytoma. However, this did not result in any meaningful improvement in survival.⁷

The recent analysis of tissue obtained from a variety of sources by different groups has shown conclusively that primary brain tumors in children have distinct features when compared to adult gliomas.^{1,4,12,15} Furthermore, the majority of DIPGs have a particularly unique molecular signature, that of mutations in the histone genes, which leads to changes in gene expression that are believed to account for their oncogenesis.^{3,9,14} In addition, pharmacological alterations in histone methylation appear to result

in inhibition of tumor growth, at least in preclinical studies.^{5,6}

The biological advances as well as the surgical techniques that have been present for the last 10–20 years have allowed biopsies to be performed with acceptable morbidity.^{2,11} In the series published to date, the majority of complications were transient cranial neuropathies, although more serious ones have been reported. Although the potential for surgical morbidity cannot be ignored or minimized, there is a path forward in terms of the molecular and biological characterization of DIPGs that can be used to further refine therapeutic decisions¹⁰: specifically, biopsy-directed clinical trials that use tissue to assign patients to rational therapeutic arms are under way.

Recently opened trials using advanced sequencing techniques to identify molecular alterations within specific pathways for a patient's tumor have allowed therapy to be directed against those targets—an example of personalized medicine (clinicaltrials.gov NCT01182350 and NCT02233049). Of course, it is not clear whether this approach casts too broad a net, or whether other factors such as inadequate drug delivery will lead to failure. However, within the broader scope of precision medicine, and perhaps uniquely for children with rare cancers, continued development of rationally designed clinical trials is needed. In an era of rapid acquisition of RNA and DNA deep sequencing information in individual cases, “rational” means using tumor-derived molecular information wisely. Strategies that use genomic data within individual patients are ongoing in the treatment of most cancers, including adult glioma and now, hopefully, in children within all subsets of CNS tumors. Tumor tissue is a requirement to achieve these goals.

Resection and/or biopsy of tumors located in many other eloquent regions of the brain such as the thalamus, insula, perisylvian location, and in the spinal cord are considered the standard of care. Whereas most neurosurgeons would consider biopsy of other areas of the brain acceptable, this perspective is generally not applied to patients

with DIPG. At this point, the ability to identify biological subtypes with rapid genomic profiling linked to potentially actionable therapeutics, and a clear understanding of surgical risk, provide a justification for considering and not fearing the option of surgical biopsy. For most centers, this means that surgical biopsy in the context of an approved and rational clinical trial with experienced neurosurgeons should be viewed as the standard of care for this disease.^{8,13}

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Disclosures

The authors report no conflict of interest.