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REVIEW ARTICLE

Re-Examining the Need for Tissue Diagnosis in Pediatric Diffuse Intrinsic Pontine Gliomas: A Review

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Abstract: Diffuse intrinsic pontine glioma (DIPG) is a malignant brain tumor of childhood that carries an extremely poor prognosis. There are ~200-300 new cases diagnosed each year, [1, 2] and little progress has been made in changing the prognosis and outcome of the tumor since it was first documented in the literature in 1926 [3]. The median overall survival is 8-11 months [4], with an overall survival rate of 30% at 1 year, and less than 10% at 2 years [4]. This review will provide background information on DIPGs, a historical look at the trends in caring for DIPG, and current trends in diagnosis and treatment. By changing the way we care for these terminal tumors, we can work towards having a better understanding of the underlying molecular biology, and attempt to develop better chemotherapeutic tools to combat the disease.

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Keywords: Brainstem, brainstem glioma, DIPG, glioma, pediatric brain tumorm, pediatric neuro-oncology, pontine glioma, radio surgery.

INTRODUCTION

There are approximately 15,000 children diagnosed with cancer each year in the United States [5]. Cancer of the central nervous system is the most common solid form of pediatric cancer, comprising approximately 21% of all malignancies in children [5]. Of these, brainstem tumors make up 10-14% of all diagnosed primary CNS tumors [1]. There are ~200-300 cases of brainstem tumors diagnosed in the US each year [1], and 60-75% of these are categorized as diffuse intrinsic pontine gliomas [6]. The average age at diagnosis of DIPG is 7-9 years, with no apparent sex predilection [1, 7, 8]. This aggressive neoplasm was first reported in 1926 in a patient with rapid onset of cranial nerve palsies and pyramidal tract dysfunction who died within a few months of presentation [3]. Unfortunately, even with currently available treatment modalities, the overall survival rate of DIPG remains dismal: 30% at 1 year, and less than 10% at 2 years [4].

A significant amount of resources are currently devoted to investigating this devastating disease in an attempt to better understand the biology of DIPG and identify more effective therapies. Brainstem gliomas represent a heterogeneous group of tumors with distinct radiologic, histologic, and molecular characteristics, making categorization challenging in order to study and treat these neoplasms. This review will provide a summary of DIPGs in the literature and provide insight on current therapies and future directions in treatment.

Gliomas of the brainstem are generally classified based on anatomic location and appearance on imaging [7]. The tumors may arise from the midbrain tectum or tegmentum, pons, medulla, or cervicomedullary junction. Categorization includes diffuse or focal, and intrinsic or exophytic with respect to the brainstem [1, 2]. Up to 75% of brainstem gliomas are diffuse intrinsic pontine gliomas (DIPG) [1, 9]. While gliomas arising in the midbrain and medulla are typically low-grade lesions, DIPGs are aggressive tumors that are relatively resistant to conventional therapies and are a leading cause of brain tumor death in children. Tumor progression is common, with median overall survival of 8-11 months, and overall survival rate of 30% at 1 year, and less than 10% at 2 years [4]. Despite significant interest in developing new treatment regimens, the prognosis of a patient newly-diagnosed with DIPG has not improved over the last 30 years [4].

DIPGs typically present with a short clinical course and relatively rapid development of neurological signs and symptoms over 2-6 months. Symptoms may include long tract signs (hyperreflexia, Babinski sign, weakness), cerebellar signs (ataxia, dysmetria, dysarthria), and cranial neuropathies. The most commonly affected cranial nerves are VI and VII, and deficits may occur unilaterally or bilaterally [10, 11]. Rare long-term survival (2-3%) has been reported, with these patients often exhibiting atypical imaging characteristics and clinical features such as young age at presentation, and long latency between onset of symptoms and diagnosis [4, 12-14].

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MRI is the diagnostic modality of choice when investigating brainstem gliomas. The typical radiographic appearance of DIPG is an expansile hypertrophic and diffuse infiltrative lesion of the ventral pons. It appears hypointense on T1-weighted images, and hyperintense on T2 and FLAIR sequences [11]. These tumors have indistinct margins and usually demonstrate minimal to no enhancement with gadolinium [11]. There may be regions of cystic necrosis and extension along white matter tracts into the cerebellum, midbrain, cerebrum, medulla, or cervical spinal cord. There have also been reports of tumor dissemination with leptomeningeal enhancement [15, 16]. PET scans may be helpful for determining high-grade vs. low-grade gliomas [17-19] and diffusion tensor imaging can help identify degeneration of white mater tracts and play a role in identifying tumor extension into adjacent tissue [20-22].

DIAGNOSIS

In order to diagnosis a brain tumor and guide post-surgical adjuvant therapy, a biopsy to obtain tissue is usually required. Due to the precarious location and aggressive pathology of DIPGs, obtaining a tissue diagnosis can be challenging. Historical literature reports high operative morbidity and mortality, which is unacceptable to most surgeons wanting to preserve quality of life and function in patients with this condition and its extremely poor prognosis. A diagnosis based on a small sample obtained from a biopsy may reflect a sampling error and not represent the tissue of the entire tumor, thus not guiding adjuvant therapy appropriately. Modern MRI techniques provide high quality radiologic studies that may establish diagnosis with certainty by imaging alone, therefore potentially alleviating the need for tissue diagnosis [8].

Because of this, in 1990 Barkovich *et al* devised radiologic criteria based on MRI for diagnosis of brainstem gliomas [17]. In 1993 another group similarly recommended that MRI should replace routine tissue biopsy for diagnosis of diffuse brainstem gliomas because of the relatively high specificity of appearance on MRI of these lesions [23]. Another study in 2007 showed that by comparing MRI with biopsy results, a diagnosis of a brainstem tumor could be made with specific imaging criteria, clinical history, and laboratory data with 94% sensitivity and 43% specificity with a positive predictive value of 96% [24]. In brainstem gliomas, radiographic determination correlated with World Health Organization (WHO) grade in up to 74% of cases [24]. Therefore, the diagnosis of a pediatric brainstem glioma could be made on the basis of imaging alone, and biopsies became reserved for atypical lesions [24].

Brainstem primitive neuroectodermal tumors (PNET)s can mimic DIPGs radiographically, with post-mortem studies revealing a histologic diagnosis of PNET in as many of 22% of patients [25]. The prognosis is not drastically different from DIPG, but long-term survival has been reported with a combined modality therapy that includes intensive chemotherapy and focal irradiation [26].

Resulting from this trend toward diagnosing DIPGs based on imaging alone without obtaining tissue, the primary source of tissue for investigations into the biology of DIPGs was largely surmised from pediatric high-grade gliomas from the supertentorial region, or autopsies, which may not represent the true biology of an *in vivo* tumor at the time of diagnosis. More recently there has been a study suggesting that MRI cannot predict prognosis in children with DIPG without correlation to histological findings or treatment response [27]. In addition, in the era of stereotactic-guided surgical procedures, the idea of foregoing a biopsy in the treatment algorithm of DIPG treatment is being reconsidered. A European study contends that stereotactic biopsies of diffuse pontine tumors are a safe procedure associated with minimal morbidity with a high diagnostic yield that can guide therapy [28].

Due to modern surgical techniques and the availability of tools including operative microscopes, stereotactic technology, and corticosteroids, the operative risk of brainstem biopsies has greatly reduced. Biopsies are safe to preform and can aid in identifying children who should be treated more or less aggressively according to their prognosis based on histopathologic investigation [9]. A European group of pediatric neurosurgeons came to an agreement on when to perform surgery in pediatric patients with brainstem gliomas. The second Consensus Conference on Pediatric Neurosurgery held in 2011 concluded with the creation of Consensus Statements to guide surgical decision-making. In regards to a typical DIPG, the group contends that a biopsy is justified when the patient is part of an ethically approved clinical study in which the tissue obtained will be used to investigate or inform the role of biological markers after treatment selection or molecular tumor grading [29]. For atypical pontine region tumors, the authors recommend a biopsy by an experienced pediatric neurosurgeon is indicated to confirm the diagnosis and guide therapy, and an atypical pontine region tumor is considered separately from classic DIPG for therapy or research purposes [29].

Biopsy of children with suspected DIPG based on history and MRI appearance has been performed in Europe since 2003 [28]. The authors report successful biopsies in 24 children with experiencing morbidity in 2 patients (cranial nerve palsy, worsening hemiparesis which was reversible), with no mortalities [28]. By demonstrating the relative safety of modern neurosurgical techniques, and the ability to perform genomic testing on small tissue samples allowing the identification of potential drug targets, there is a movement in the pediatric neuro-oncology community to push for biopsy of patients with suspected DIPG, but it still remains under debate [30-32]. Currently in the United States there is a multi-center trial that involves an upfront biopsy of cases of suspected DIPG [33]. The tissue obtained undergoes molecular analysis in order to plan a treatment strategy for each individual patient.

TREATMENT

The standard of therapy for DIPG treatment remains radiation therapy [4]. The dose is between 5,400 and 6,000 cGy given in 180-200cGy daily fractions. It may provide clinical improvement in up to 70% and objective tumor response in 40-60%, [34] but does not improve overall survival [1]. There has been no benefit shown with hyperfractionated radiation versus conventional radiation

dosing [35]. Radiation at higher doses has shown increased toxicity without improvement in outcome [36]. There have been studies suggesting that hypofractionation may be equal or nearly equivalent in efficacy to conventional radiation therapy with decreased treatment burden [37]. Attempts have been made to use chemotherapeutic agents prior to radiation such as cisplatin [35] and motexafin gadolinium [38] but no evidence of benefit was found. One of the challenges of studying DIPG response to radiation is that there is limited availability of animal models, and therefore researchers are highly reliant on autopsy material to use for their investigations. The samples are often obtained after radiation treatment, which can alter the biology of the tumor thus not reflecting the true nature of DIPGs.

There have also been multiple trials showing no benefit of adding conventional cytotoxic chemotherapy to radiation therapy in the treatment of DIPGs. Trials using cytotoxic agents in various combinations with diverse dosing intensities including myeloablative chemotherapy with stem cell rescue have been attempted [39, 40]. A recent trial reveled that temozolomide had no benefit in DIPG treatment compared to historical controls treated with radiation alone [41]. Other trials of chemotherapeutic agents have also had disappointing results including tamoxifen [42] and beta-interferon [43].

DISCUSSION

Because diagnosis of DIPG has been made based on MRI findings rather than obtaining tissue, biologic advances in DIPG treatment have been challenging. Tumors that were diagnosed by biopsy were traditionally atypical cases which may not reflect true DIPG biology [29]. Many centers have strived to obtain post-mortem specimens from DIPG patients providing new insights into DIPG biology over the past decade [25, 44]. Perhaps most promising is the identification of whole genome sequencing that has identified a unique histone 3.3 (H3F3A) K27M mutation in a majority of DIPGs and a subset of pediatric glioblastoma [44-47]. Another protein of interest, PARP [Poly(ADP-ribose)] polymerase, has been found to be overexpressed in certain DIPG cells. This enzyme normally allows cells to fix DNA damage, and may potentially aid tumor cells in nullifying the effects of radiation and chemotherapy treatment. A study called PBTC-033 is a Phase I/II clinical trial sponsored by the Pediatric Brian Tumor Consortium currently enrolling pediatric patients to investigate a new drug, ABT-888, that interferes with PARP and could potentially make DIPG more sensitive to chemotherapy and radiation [48].

Post-treatment and post-mortem samples, however, have their limitations. The molecular characteristics may be vastly different from the primary untreated tumor because of accumulation of bystander mutations and the selective pressures of radiation and chemotherapy [49, 50]. Because of these limitations, there is widespread renewed interest in obtaining pre-treatment samples. Specialized centers have the ability to use current surgical techniques to obtain a tissue biopsy of DIPG at the time of initial presentation in a safe manner for meaningful analysis [51]. In addition to confirming the histological diagnosis of DIPG, analysis of specific signaling pathways altered in a given tumor could allow targeted therapies with molecular inhibitors for the patient. This approach could potentially improve outcomes in patients with DIPG and is currently the subject of a multi-institutional trial in the United States (NCT01182350) [52].

Cytotoxic agents and other specific targeted therapies may not effectively treat DIPGs if they are unable to adequately penetrate the tumor [41]. DIPGs are thought to have an intact blood-brain barrier, which is supported by the fact they have limited contrast enhancement on MRI scans [23]. This phenomenon is a target of investigation, and analysis of pre- and post-treatment DIPG specimens has demonstrated that multiple major drug-efflux pumps are typically expressed in the tumor vasculature [53]. This is a potential area to exploit in the investigation of direct delivery of antineoplastic agents to the tumor *via* convection-enhanced delivery [54, 55]. Convention-enhanced deliver (CED) seeks to overcome some of the difficulties encountered when pharmacological agents try to cross the blood-brain barrier. Drugs are delivered through catheters placed within or around a tumor mass or resection cavity, often with stereotactic guidance [56].

CONCLUSION

Diffuse intrinsic pontine glioma is a disease for which diagnosis, treatment, and prognosis has changed little over time, despite hundreds of papers published on the topic, reflecting the large amount of work focused on the issue. By applying resources toward safely obtaining pre-treated neoplastic tissues to investigate, we may make progress in this relentless adversary. This is a diagnosis fraught with intense emotions experienced by families that have to address this devastating disease. One of the big challenges to Neuro-Oncologists and Neurosurgeons is how to counsel families and advise them to undergo a surgery that may not necessarily help their child, but may one day help children in the future survive this terminal diagnosis. With the evolution of clinical trials, parents may now be given the choice to do a biopsy that can identify the individual characteristics of their child's tumor and chose the chemotherapeutic agents that are most effective. Only by gaining additional molecular information about these tumors will we be able to make a change in the outcome of this terminal disease.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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