



# Treatment Limitations for Pediatric Diffuse Intrinsic Pontine Gliomas in a Middle-Income Country

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## Abstract

**Objectives** To evaluate the surgical management outcomes in pediatric patients with diffuse intrinsic pontine gliomas (DIPGs) who underwent intended biopsies and partial resections in a middle-income country, highlighting the barriers and challenges of these procedures for further investigation.

**Methods** A retrospective review of a prospective acquired series of patients who underwent biopsy or resection for DIPG between January 2012 and June 2018 at our institution was performed.

**Results** A total of 43 patients with posterior fossa tumors were identified. From these, seven pediatric DIPG cases were enrolled. Five were males. The median age was 5 years (range: 1–12 years). Only one patient (14.3%) had a ganglioglioma, while the others presented pilocytic and diffuse astrocytomas. Two (28.6%) patients had an intentional biopsy, and the other five (71.4%) had a partial resection. In the three (28.6%) patients who presented with associated hydrocephalus, the endoscopic third ventriculostomy was performed in the same surgical time. The median preoperative Lansky play-performance scale (LPPS) was 80 (range: 60–100), while the median postoperative LPPS was 23 (range: 7–52).

**Conclusion** A decrease in overall survival was noted compared with data reported in other series. Multifactorial barriers were discussed including the social, geographic, and economic features that may influence on final outcomes.

## Keywords

- brain stem
- neurosurgeon
- pediatric
- diffuse intrinsic pontine glioma

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## Introduction

Diffuse intrinsic pontine gliomas (DIPGs) are high-grade brain stem gliomas accounting for ~10 to 20% of all pediatric brain tumors.<sup>1</sup> Annually ~200 to 300 children are diagnosed with DIPG in the United States. DIPG typically occurs between 6 and 9 years of age.<sup>2</sup> It is the leading cause of childhood mortality due to central nervous system (CNS) malignancies with a median overall survival (OS) ranging from 8 to 12 months. More than 50% of patients experience cranial nerve, cerebellar, and long tract impairments. DIPG diagnosis is challenging; although biopsy or resection allows a histopathological classification, deciding whether to perform an invasive approach or not must be made on a case-by-case manner. Currently, a discussion remains on the feasibility and safety of a brain stem biopsy, arguing the benefit of molecular characterization for management, reducing the mortality rate, potential drug discovery, and investigation purposes against patients' risks. Besides those cases when an intentional biopsy is indicated, diagnosis may be conducted through only imaging criteria, laboratories, and a detailed clinical history. MRI reaches overall sensitivity of 94% and has proven its utility for tumor classification and prognosis.<sup>3–6</sup> Furthermore, the imaging-based diagnosis and clinical history still face significant variations among neurosurgeons and neuro-oncologists, rekindling the debate on stereotactic biopsy when diagnosing and deciding further treatment.<sup>7</sup>

Management decision keeps evolving as more biomarkers and molecular research are conducted to develop targeted therapies.<sup>7</sup> However, advances in treatment have not reached a meaningful improvement in OS and no curative options are available yet.<sup>8</sup> This case series aim to evaluate the surgical management outcomes in pediatric patients with DIPG through a retrospective review of a prospective acquired cases series including biopsies and intended partial resections in a middle-income country (MIC), highlighting the barriers and challenges of these procedures for further investigation.

## Methods

A retrospective review of the electronic medical records of patients who underwent biopsy or resection for DIPG between January 2012 and June 2018 at the Hospital Infantil Universitario de San José, Bogotá, Colombia was performed. Data corresponded to procedures performed by a dedicated pediatric neurosurgeon (P.E.B.). Database review was performed based on surgical codes. The exclusion criteria included: aged 18 or older, brain tumors different from DIPG, patients diagnosed or treated previously in a different institution, and patients who underwent procedures other than biopsy or tumor resection. All procedures were performed using a freehand frameless image-guided technique. Surgical features were described previously.<sup>9</sup> The following data were collected: sex, age, clinical presentation at diagnosis, histopathological classification, tumor localization, as well as surgical and adjuvant treatments. The primary outcomes

were the postoperative Lansky play-performance scale (LPPS) for children score, hospital length of stay (LOS), and OS. Our institutional research ethics committee approved this retrospective study. Authorization was requested to our institutional ethics board to include the subjects' information in this study, preserving their identity in analyzing the data and all images presented. Given the retrospective nature of this study, the ethics committee considered a low risk from this research for the patients and no informed consents were required for this study accordingly.

## Results

A total of 43 patients with posterior fossa tumors were identified. From these, seven pediatric DIPG cases were enrolled. Patients included five males and two females with a median age of 5 years (range: 1–12 years). Symptoms preceded diagnosis by a median of 42 weeks (range: 1–108 weeks). New daily persistent headache was the most common reason for consultation, experienced by four patients (42.9%). Other features at admission included nausea and vomiting, upper limb paresis, hemiparesis, hemisensory syndrome, cyanotic breath-holding spells, psychomotor developmental delay, diplopia, dysconjugate gaze, and blepharoptosis. Besides previous features, hydrocephalus was reported in three patients (42.9%). Diagnosis was initially based on imaging criteria in all cases. All patients presented a diagnosis of low-grade glioma. Only one patient (14.3%) had a ganglioglioma, while the others presented pilocytic and diffuse astrocytomas. Complete immunophenotype report was only available for patients 1 and 5. Patient 1 presented positivity for glial fibrillary acidic protein (GFAP) and epithelial membrane antigen (EMA), while patient 5 presented positivity for GFAP, oligodendrocyte transcription factor 2, and synaptophysin and S-100 protein. For the remaining cases, the sample was insufficient to process additional immunophenotype data. ►Table 1 summarizes the clinical features of the patients.

Two (28.6%) patients had an intentional biopsy, and the other five (71.4%) had a partial resection. In the three (28.6%) patients who presented with associated hydrocephalus, the tumor biopsy/resection and an additional endoscopic third ventriculostomy were performed in the same surgical time. Regarding nonsurgical treatment, three (28.6%) patients received chemotherapy and radiotherapy, while the other four (57.1%) only received radiotherapy based on the pediatric oncologist recommendation. In general, there was an overall decrease in the LPPS after both biopsy and partial resection. The median preoperative LPPS was 80 (range: 60–100), while the median postoperative LPPS was 23 (range: 7–52); there was a median reduction of 10 points in the LPPS (range: 10–40). The median medical LOS was 18 days (range: 6–35 days), and six (85.7%) patients required postoperative care in the pediatric intensive care unit (ICU), with a median ICU stay of 3 days (range: 1–8 days). Median survival was 23 days (range: 7–52 days). ►Table 2 summarizes the surgical outcomes of each patient and the corresponding follow-up.

**Table 1** Clinical characteristics of patients with DIPG

| Patient        | Sex | Age (y) | Clinical presentation                                             | Location           | Hydrocephalus | Histopathological classification | Nonsurgical treatment        |
|----------------|-----|---------|-------------------------------------------------------------------|--------------------|---------------|----------------------------------|------------------------------|
| 1              | F   | 11      | Headache                                                          | Lower medulla      | No            | Pilocytic astrocytoma            | Chemotherapy<br>Radiotherapy |
| 2              | M   | 12      | Headache<br>Nausea and vomiting                                   | Pons               | No            | Low-grade astrocytoma            | Chemotherapy<br>Radiotherapy |
| 3              | M   | 1       | Upper limb paresis<br>Hemisensory syndrome                        | Lower medulla      | No            | Pilocytic astrocytoma            | Radiotherapy                 |
| 4              | M   | 4       | Cyanotic breath-holding spells<br>Psychomotor developmental delay | Lower medulla      | No            | Diffuse astrocytoma              | Chemotherapy<br>Radiotherapy |
| 5 <sup>a</sup> | F   | 5       | Headache                                                          | Pons               | Yes           | Ganglioglioma                    | Radiotherapy                 |
| 6 <sup>a</sup> | M   | 12      | Diplopia<br>Dysconjugate gaze<br>Third cranial nerve palsy        | Posterior midbrain | Yes           | Diffuse astrocytoma              | Radiotherapy                 |
| 7 <sup>a</sup> | M   | 4       | Hemiparesis                                                       | Midbrain           | Yes           | Diffuse astrocytoma              | Radiotherapy                 |

Abbreviation: DIPG, diffuse intrinsic pontine glioma.

<sup>a</sup>Documented hydrocephalus.**Table 2** Surgical management and clinical outcomes of patients with DIPG

| Patient | Type of surgery    | Surgical approach          | Tumor volume (mL) | Medical LOS (d) | ICU LOS (d) | Preoperative LPPS score | Postoperative LPPS score | Survival (d) |
|---------|--------------------|----------------------------|-------------------|-----------------|-------------|-------------------------|--------------------------|--------------|
| 1       | Partial resection  | Far lateral                | 2.81              | 9               | 2           | 100                     | 90                       | 43           |
| 2       | Partial resection  | Far lateral                | 4.54              | 23              | 1           | 60                      | 50                       | 52           |
| 3       | Partial resection  | Far lateral                | 10.18             | 6               | 4           | 70                      | 60                       | 22           |
| 4       | Partial resection  | Retrosigmoid               | 6.39              | 18              | 0           | 80                      | 60                       | 7            |
| 5       | Partial resection  | Retrosigmoid and ETV       | 24.02             | 17              | 1           | 80                      | 60                       | 23           |
| 6       | Intentional biopsy | Ventricular biopsy and ETV | 21.29             | 35              | 8           | 90                      | 50                       | 50           |
| 7       | Intentional biopsy | Ventricular biopsy and ETV | 21.74             | 18              | 4           | 70                      | 60                       | 20           |

Abbreviations: DIPG, diffuse intrinsic pontine glioma; ETV, endoscopic third ventriculostomy; ICU, intensive care unit; LOS, length of stay; LPPS, Lansky play-performance scale.

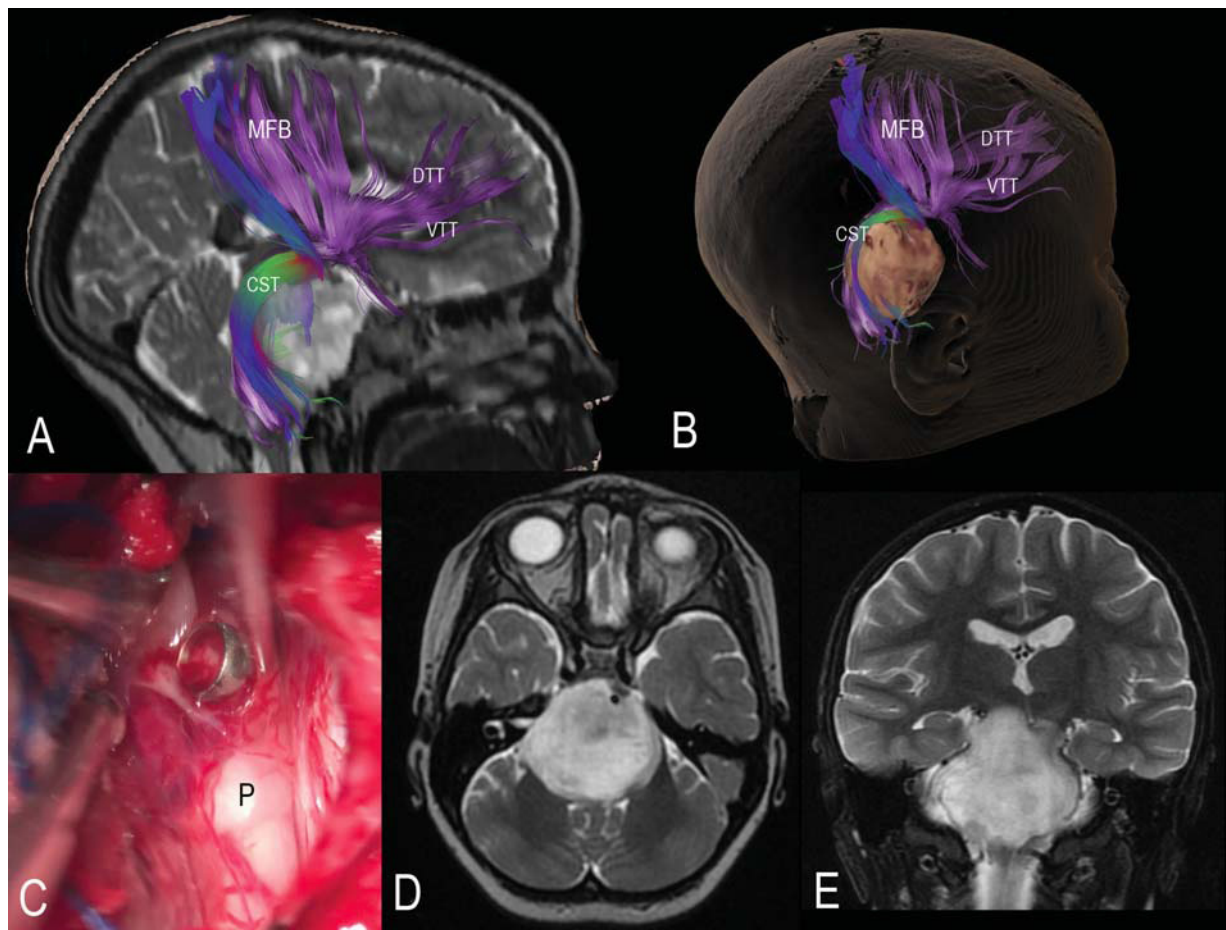
## Discussion

DIPG remains the leading cause of death due to a brain tumor in pediatric patients. Despite clinical trials over the past years, OS persists low, and most children die within 2 years after diagnosis.<sup>10</sup> Symptoms result from the mass effect and underlying dysfunction about the ventral pons. Major critical pathways are involved with these tumors, including nuclei and tracts of vital human functions, long pathways, and most of cranial nerves nuclei. An illustrative tractography demonstrating displacement of the ascending arousal network and the corticospinal tracts is demonstrated in ►Fig. 1. Consequently, major clinical deficits lead patients to a rapid functional decline and decease.

Currently, radiotherapy (standard fractionated radiation alone) remains the standard of care and multiple treatments have been investigated to achieve additional overwhelming benefit, including multiple chemotherapy and immunotherapy regimens.<sup>11</sup> Radiotherapy alone results in temporary neurological improvement without a substantial change in OS. Surgical resection is not an option in most cases and

neither provides significant improvements in OS.<sup>12</sup> Although there is no significant advance in the surgical management of DIPG over the past decades, stereotactic biopsy has gained some attention, especially for research purposes. Obtaining samples contribute to a better understanding of the molecular basis to develop new targeted therapies.<sup>13</sup> These protocols have led to identifying biomarkers and crucial oncogenic pathways in DIPG pathogenesis.<sup>14</sup>

As DIPG is diffusely infiltrative, complete resection results almost impossible and there is a risk for severe neurologic sequelae.<sup>15</sup> It has been acknowledged that some selected cases may benefit from attempting resection or debulking of low-grade tumors. However, ~8% of brain stem biopsies may result in any new-onset deficit.<sup>16</sup> A meta-analysis including 735 stereotactic biopsies for pediatric brain stem tumors reported 6.7% for overall morbidity, 0.6% for permanent morbidity, and 0.6% for mortality.<sup>17</sup> However, as the treatment of DIPG is radiotherapy alone in many centers worldwide, this study contributes with five cases in which partial resection was intended, and the outcomes were assessed.



**Fig. 1** Reconstruction of the ascending arousal network and corticospinal tract (CST) for diffuse intrinsic pontine glioma surgical planning. (A) Lateral view of T2-weighted volumetric imaging and (B) three-dimensional reconstruction of the volumetric magnetic resonance imaging demonstrating a distorted anatomy of long tracts, showing posterior displacement of the CST and the ascending arousal network fibers including those from the middle forebrain bundle (MFB), dorsal tegmental tract (DTT), and ventral tegmental tract (VTT). (C) Intraoperative image demonstrating a retrosigmoid approach with exposure of the inferolateral aspect of the pons (P) and the debulking through the lateral pontine safe entry zone. (D, E) Axial and sagittal T2-weighted images showing a hyperintense diffuse intra-axial expansive pontine lesion.

### Challenges and Barriers for DIPG Treatment in a MIC Setting

Despite multiple efforts made to improve outcomes of DIPG patients worldwide, there is lack of consensus of a standard treatment protocol.<sup>18</sup> Additionally, a big concern remains of DIPG treatment in MICs, where multiple limitations influence on the final outcome.<sup>19</sup> DIPG remains an orphan disease in MICs, and the registry and documentation of the evolution of the disease is scarce.

From these five cases with partial resection, OS was considerably lower than reported from a DIPG biopsy where median OS has been estimated between 6 and 14 months after the procedure.<sup>20</sup> Both subgroups, partial resection and biopsy experienced an overall reduction in the LPPS. A higher decline in LPPS may be appreciated in those patients with partial resection. Due to the number of patients recorded in this series, no firm conclusions could be drawn between the clinical outcomes between biopsy and intended resection. Final outcomes are related to a multifactorial environment including the middle-income economy of the health care system, the poor education of the parents, and the evident low access to pediatric neurosurgeons.

To note, the access to pediatric reference centers is limited in MICs and a delayed attention to CNS malignancies is not infrequent in this scenario. Unfortunately, the impact of a delayed consultation is reflected directly on the OS and immediate postoperative outcome. In terms of litigations in our country, radiotherapy is restricted only to patients with confirmed histopathological diagnosis and, consequently, to initiate adjuvant treatment, a biopsy or an intended resection is always required. In addition, 2 to 3 weeks after sample acquisition are needed to establish a definite diagnosis of DIPG. Usually, the samples are insufficient for running all complementary tests. This study was performed before the access to molecular studies was available in our setting. In further cases, the molecular profile will help physicians in MICs to approach in a holistic personalized manner, the targeted therapies to improve OS.

Additional to the limited resources, neurosurgeons and patients' families face the limited access to pediatric clinical oncologists and radiotherapeutic oncologists. The poor networking among specialties also limits the multidisciplinary treatment needed for this complex entity and lead to a poorer prognosis. Data concerning outcomes and epidemiology of DIPGs are restricted for MICs, probably as a consequence of lack of data given the high probability to die during this long process before treatment of even before an initial medical consultation.

Regarding surgical treatment, availability for renting neuronavigation systems and the access to advanced neuroimaging including diffusion tensor imaging have allowed some progress aiming to reduce neurological decline after procedures.<sup>9</sup> Most likely, rapid progression of disease is produced by the notable advanced stages when these tumors are detected and not directly related to the procedure itself. We hope this case series will add remarkable information and will promote the initiative to improve clinical care of this neglected disease in MICs.

### Study Limitations

The limited number of cases as well as the retrospective nature of this study represent the most remarkable limitations. However, even with few cases, the information is an important basis for further epidemiological characterization of the disease. No data in regard to epigenetics are described given the lack of institutions and equipment for processing.

### Conclusion

A case series of patients with DIPG in a MIC is presented. A decrease in OS was noted compared with data reported in other series. Multifactorial barriers were discussed including the social, geographic, economic, and education features that may influence on the final outcomes of patients. Pediatric neurosurgeons are encouraged to describe other limitations and clinical features in other MICs that may help understand problematics and make an improvement of DIPG treatment.

#### Funding

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#### Conflict of Interest

None declared.

### References

- 1 Janjua MB, Ban VS, El Ahmadi TY, et al. Diffuse intrinsic pontine gliomas: diagnostic approach and treatment strategies. *J Clin Neurosci* 2020;72:15–19
- 2 Fisher PG, Breiter SN, Carson BS, et al. A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. *Cancer* 2000;89(07):1569–1576
- 3 Broniscer A, Laningham FH, Kocak M, et al. Intratumoral hemorrhage among children with newly diagnosed, diffuse brainstem glioma. *Cancer* 2006;106(06):1364–1371
- 4 Cage TA, Samagh SP, Mueller S, et al. Feasibility, safety, and indications for surgical biopsy of intrinsic brainstem tumors in children. *Childs Nerv Syst* 2013;29(08):1313–1319
- 5 Pfaff E, El Damaty A, Balasubramanian GP, et al. Brainstem biopsy in pediatric diffuse intrinsic pontine glioma in the era of precision medicine: the INFORM study experience. *Eur J Cancer* 2019;114:27–35
- 6 Schumacher M, Schulte-Mönting J, Stoeter P, Warmuth-Metz M, Solymosi L. Magnetic resonance imaging compared with biopsy in the diagnosis of brainstem diseases of childhood: a multicenter review. *J Neurosurg* 2007;106(2, Suppl):111–119
- 7 Hankinson TC, Campagna EJ, Foreman NK, Handler MH. Interpretation of magnetic resonance images in diffuse intrinsic pontine glioma: a survey of pediatric neurosurgeons. *J Neurosurg Pediatr* 2011;8(01):97–102
- 8 Khatua S, Zaky W. Diffuse intrinsic pontine glioma: time for therapeutic optimism. *CNS Oncol* 2014;3(05):337–348
- 9 Ordóñez-Rubiano EG, Valderrama-Arias FA, Forbes JA, et al. Identification of preoperative language tracts for intrinsic frontotemporal diseases: a pilot reconstruction algorithm in a middle-income country. *World Neurosurg* 2019;125:e729–e742
- 10 Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. *Lancet Oncol* 2006;7(03):241–248

- 11 Srikanthan D, Taccone MS, Van Ommeren R, Ishida J, Krumholtz SL, Rutka JT. Diffuse intrinsic pontine glioma: current insights and future directions. *Chin Neurosurg J* 2021;7(01):6
- 12 Frazier JL, Lee J, Thomale UW, Noggle JC, Cohen KJ, Jallo GL. Treatment of diffuse intrinsic brainstem gliomas: failed approaches and future strategies. *J Neurosurg Pediatr* 2009;3(04):259–269
- 13 Williams JR, Young CC, Vitanza NA, et al. Progress in diffuse intrinsic pontine glioma: advocating for stereotactic biopsy in the standard of care. *Neurosurg Focus* 2020;48(01):E4
- 14 Lapin DH, Tsoli M, Ziegler DS. Genomic insights into diffuse intrinsic pontine glioma. *Front Oncol* 2017;7:57
- 15 Mathew RK, Rutka JT. Diffuse intrinsic pontine glioma: clinical features, molecular genetics, and novel targeted therapeutics. *J Korean Neurosurg Soc* 2018;61(03):343–351
- 16 Hersh DS, Kumar R, Moore KA, et al. Safety and efficacy of brainstem biopsy in children and young adults. *J Neurosurg Pediatr* 2020;26(05):552–562
- 17 Hamisch C, Kickingeder P, Fischer M, Simon T, Ruge MI. Update on the diagnostic value and safety of stereotactic biopsy for pediatric brainstem tumors: a systematic review and meta-analysis of 735 cases. *J Neurosurg Pediatr* 2017;20(03):261–268
- 18 Lian X, Kats D, Rasmussen S, et al. Design considerations of an IL13R $\alpha$ 2 antibody-drug conjugate for diffuse intrinsic pontine glioma. *Acta Neuropathol Commun* 2021;9(01):88
- 19 Ezzat S, Kamal M, El-Khateeb N, et al. Pediatric brain tumors in a low/middle income country: does it differ from that in developed world? *J Neurooncol* 2016;126(02):371–376
- 20 Wang ZJ, Rao L, Bhambhani K, et al. Diffuse intrinsic pontine glioma biopsy: a single institution experience. *Pediatr Blood Cancer* 2015;62(01):163–165