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CLINICAL STUDY

# Pontine gliomas a 10-year population-based study: a report from The Canadian Paediatric Brain Tumour Consortium (CPBTC)

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## Abstract

**Background** Diffuse intrinsic pontine gliomas (DIPG) are midline gliomas that arise from the pons and the majority are lethal within a few months after diagnosis. Due to the lack of histological diagnosis the epidemiology of DIPG is not completely understood. The aim of this report is to provide population-based data to characterize the descriptive epidemiology of this condition in Canadian children.

**Patients and methods** A national retrospective study of children and adolescents diagnosed with DIPG between 2000 and 2010 was undertaken. All cases underwent central review to determine clinical and radiological diagnostic characteristics. Crude incidence figures were calculated using age-adjusted (0–17 year) population data from Statistics Canada. Survival analyses were performed using the Kaplan–Meier method.

**Results** A total of 163 patients with pontine lesions were identified. Central review determined one-hundred and forty-three patients who met clinical, radiological and/or histological criteria for diagnosis. We estimate an incidence rate of 1.9 DIPG/1,000,000 children/year in the Canadian population over a 10 years period. Median age at diagnosis was 6.8 years and 50.3% of patients were female. Most patients presented with cranial nerve palsies (76%) and ataxia (66%). Despite typical clinical (i.e. long length of symptoms) and radiological characteristics, (i.e. focal tumors, tumors with exophytic components or cystic components) histological confirmation reported three lesions to be low-grade gliomas and three were diagnosed as CNS embryonal tumor not otherwise specified (NOS).

**Conclusions** Our study highlights the challenges associated with epidemiology studies on DIPG and the importance of central review for incidence rate estimations. It emphasizes that tissue biopsies are required for accurate histological and molecular diagnosis in patients presenting with pontine lesions and reinforces the limitations of radiological and clinical diagnosis in DIPG. Likewise, it underscores the urgent need to increase the availability and accessibility to clinical trials.

**Keywords** Diffuse intrinsic pontine glioma (DIPG) · Epidemiology · Brainstem tumors · H3K27M

## Introduction

Diffuse intrinsic pontine gliomas (DIPG) are midline gliomas that arise from the pons and are lethal within a few months after diagnosis [1]. Patients diagnosed with DIPG usually present with a short history of symptoms suggestive of cranial nerve involvement, long tract signs, and cerebellar deficits [2, 3]. The classical magnetic resonance imaging (MRI) finding of a diffuse infiltration of the pons, engulfment of the basilar artery and lack or poor enhancement after gadolinium administration, confirms the clinical suspicion of one of the most devastating diagnoses in childhood cancer [1, 4]. Due to their critical location, the potential risk of significant morbidity associated with biopsy [5], and the lack of therapeutic options available; clinical and radiological criteria have been traditionally considered sufficient for diagnosis [6, 7].

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Historically, due to the lack of biological tissue in this entity, the biological and molecular characterization of DIPG was stalled for many years. Patients presenting with atypical clinical or radiological features were usually biopsied, providing some preliminary understanding of the histology and biology of this tumor [1, 8, 9]. With the advances in stereotactic and neuro-navigation techniques, and the increasing understanding of clinical and molecular heterogeneity within pathological entities, many centers now perform routine diagnostic biopsies, especially those with an associated clinical trial that requires a tissue diagnosis as an inclusion criterion [5, 10–13]. Over the last decade, major leaps in the understanding of the histological and mutational landscape of DIPG have been made [8, 9, 14, 15]. Recurrent mutations in position 27 of histone 3 (H3.1 or H3.3) have been identified as the defining molecular alteration in midline gliomas [1] and led to the inclusion in the World Health Organization (WHO) classification [16] as a molecularly defined entity.

Due to the lack of histological diagnosis and the use of clinical and radiological diagnostic criteria over the years, the epidemiology of DIPG is not completely understood. Large cancer registries have captured and described the incidence of DIPG and it is estimated that DIPG accounts for approximately 10% of all paediatric brain tumors [17]. Between 20 and 30 newly diagnosed DIPG occur in children annually in the UK and approximately 100–400 per year in USA [17–19]. However, no proper epidemiology study has ever been conducted.

Canada has a government-funded health care system. Children with brain tumours are treated at specialized university-affiliated teaching hospitals. The Canadian Paediatric Brain Tumour Consortium (CPBTC) was created to ensure representation from all the Canadian paediatric-neuro-oncology programs. To better understand the descriptive epidemiology of this condition, the members of the CPBTC initiated a retrospective national epidemiology study of DIPG for the period 2000–2010, thus, capturing all childhood and adolescent cases of DIPG.

## Material and methods

After Research Ethics Board approval, all seventeen paediatric neuro-oncology programs in Canada participated in this study. All patients with an institutional diagnosis of DIPG from January 2000 to December 2010 were identified and data were retrospectively collected using a standardized questionnaire. Only patients less than 18 years of age at the time of diagnosis were included. Demographic data, clinical presentation, T2 or axial flair MRI sequences, therapeutic interventions and outcomes were collected.

### Eligibility criteria

A central review was performed by two investigators (EB and SA). Typical clinical characteristic for diagnosis were defined as the presence of at least two classical neurological findings (long tract signs, ataxia and/or cranial nerve palsy); otherwise, the clinical presentation was considered atypical. Evaluation of radiological features for diagnosis of DIPG was performed. Radiological criteria used for diagnosis of DIPG included lesions occupying at least 50% of the pons on a T2 or axial flair sequence, engulfment of the basilar artery and no or minimal intra-tumoral enhancement post gadolinium administration. Lesion presenting with ring enhancement typically described in H3K27M mutant tumors were included. Patients presenting with typical radiological characteristics were included in this study and stratified by clinical features (Fig. 1). Patients with atypical radiological features were also assessed for eligibility. Patients with histologically proven glial tumors were included.

### Statistics

Population data estimates for children age 0–17 from 2000 to 2010 for the entire country and by province/territory were extracted from Statistics Canada; data current to July 1st, 2019 were used for analyses [20]. Due to the geographical location and catchment area of paediatric oncology centers in Canada, population was estimated and crude incidence rates were calculated and reported by regions. Atlantic Canada: includes the provinces of Newfoundland, Prince Edward Island, Nova Scotia and New Brunswick. Prairies: Included Manitoba, Saskatchewan, Alberta, Northwest Territories and Nunavut. British Columbia and Yukon included the population and cases of that province and territory, Quebec and Ontario are reported individually.

Survival analyses were performed using the Kaplan–Meier method, the log-rank was used to compare survivals between groups. All p values $< 0.05$ were considered significant. Statistical analysis was conducted using Stata 14.2 (StataCorp).

## Results

A total of 165 patients were identified. Two patients were excluded as lesions were not located in the pons. Thus, a total of 163 patients with pontine lesions were included. Patients were classified according to their clinical presentation as typical (n = 109) or atypical (n = 54). On central review, typical radiological characteristics of DIPG were seen in 128 patients (79%). Thirty-five (21%) patients presented with atypical radiological features; of these, seven

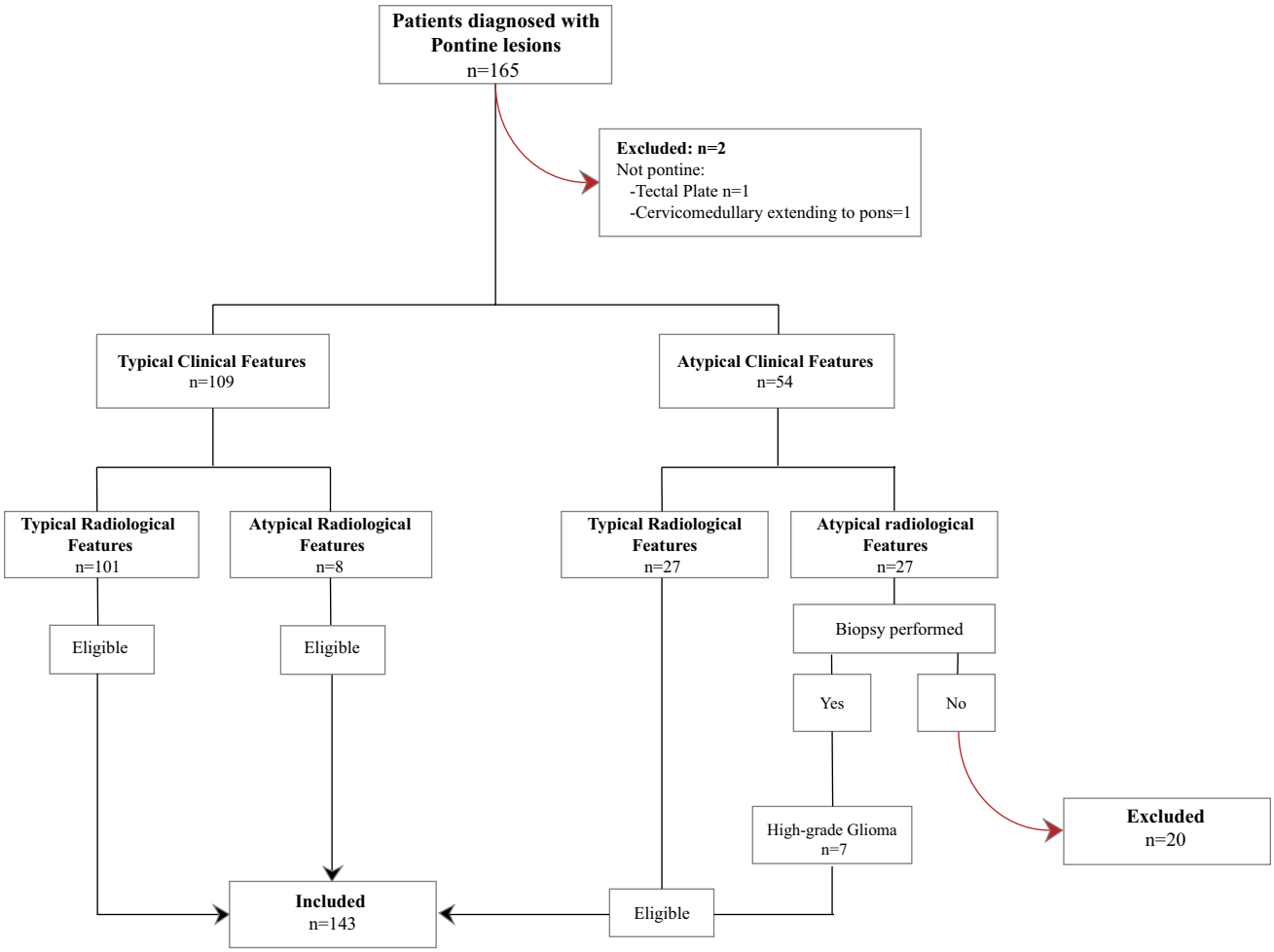



**Fig. 1** Consort Diagram demonstrating the flow of patients in this study

patients underwent biopsy and pathological diagnosis of high-grade glioma was confirmed. Twenty patients with atypical clinical (i.e. long length of symptoms) and radiological features (i.e. focal tumors, tumors with exophytic components or cystic components) didn't meet criteria for DIPG and were excluded. Of the 20 patients excluded, 19 patients are alive and 1 died of disease (Fig. 1).

One-hundred and forty-three children were included in the analysis. This number accounts for all the diagnoses of DIPG made in the paediatric Canadian population over 10 years and represents a crude incidence rate of 1.9 cases/1,000,000 children/year. The crude incidence for Atlantic Canada was 1.5/1,000,000 children/year, 1.4/1,000,000children/year in British Columbia and Yukon, and 1.2 cases/1,000,000 children/year in the Prairies region. The incidence rates in Quebec and Ontario were 2.0 and 2.3 cases/1,000,000 children/year, respectively.

Annual variations were observed, only four diagnoses in 2000 and a maximum of 23 new diagnoses 2009 were seen. However, there was no evidence of an increasing incidence in the number of cases diagnosed over this 10-year period. Three peaks of incidence were observed at a four-year interval, with 18 patients diagnosed in 2001, 18 in 2005 and 23 in 2009. No seasonal variation was observed (Table 1).

There were 71 (49.7%) males and 72 (50.3%) females. Median age at diagnosis was 6.75 years (0–17.1 years). Importantly, 116 (81%) of the patients were older than 3 years, while, only 4 (2.8%) presented before 1 year of age, including three patients diagnosed at birth (Table 2).

The time from onset of symptoms to diagnosis was available for 140 (97.2%) patients. Most of the patients, 89 (64%) presented with symptoms lasting < 6 weeks, 28 (20.2%) for 6–12 weeks, and 22 (15.8%) for > 12–24 weeks. The most common clinical symptoms in order of frequency identified at presentation were: unstable gait 88 (61%), abnormal eye movement 60 (42%), headaches 50 (35%), motor weakness 46 (32%), vomiting 38 (27%), impaired swallowing 35 (25%), speech difficulties 33 (23%) and facial asymmetry 31 (22%).

**Table 1** Canadian pediatric population (0–17 years) and age-adjusted crude incidence rates of DIPG by geographical regions

| Year | Maritimes | | | Prairies | | | BC + Yukon | | |
|---|---|---|---|---|---|---|---|---|---|
| | Population | Cases | Incidence rate[a] | Population | Cases | Incidence rate[a] | Population | Cases | Incidence rate[a] |
| 2000 | 524,790 | 1 | 0.000002 | 1,342,118 | 0 | 0.000000 | 907,247 | 2 | 0.000002 |
| 2001 | 513,200 | 0 | 0.000000 | 1,335,526 | 2 | 0.000001 | 899,554 | 1 | 0.000001 |
| 2002 | 502,005 | 1 | 0.000002 | 1,334,188 | 0 | 0.000000 | 886,863 | 2 | 0.000002 |
| 2003 | 492,139 | 1 | 0.000002 | 1,329,754 | 0 | 0.000000 | 876,460 | 1 | 0.000001 |
| 2004 | 483,034 | 1 | 0.000002 | 1,327,075 | 2 | 0.000002 | 869,861 | 0 | 0.000000 |
| 2005 | 473,625 | 1 | 0.000002 | 1,329,606 | 3 | 0.000002 | 866,966 | 2 | 0.000002 |
| 2006 | 463,803 | 0 | 0.000000 | 1,337,343 | 0 | 0.000000 | 864,500 | 1 | 0.000001 |
| 2007 | 455,917 | 1 | 0.000002 | 1,344,807 | 2 | 0.000001 | 860,309 | 2 | 0.000002 |
| 2008 | 449,189 | 0 | 0.000000 | 1,353,314 | 2 | 0.000001 | 858,165 | 1 | 0.000001 |
| 2009 | 444,177 | 2 | 0.000005 | 1,365,948 | 5 | 0.000004 | 858,552 | 1 | 0.000001 |
| 2010 | 439,985 | 0 | 0.000000 | 1,379,063 | 2 | 0.000001 | 859,221 | 0 | 0.000000 |
| Average[b] | 476,533 | 0.73 | 0.0000015 | 1,343,522 | 1.64 | 0.0000012 | 873,427 | 1.18 | 0.0000014 |
| Age-adjusted Crude Incidence Rate 2000–2010 | 1.5 × 1,000,000 children/year | | | 1.2 × 1,000,000 children/year | | | 1.4 × 1,000,000 children/year | | |

| Year | Quebec | | | Ontario | | | Canada | | |
|---|---|---|---|---|---|---|---|---|---|
| | Population | Cases | Incidence rate[a] | Population | Cases | Incidence rate[a] | Population | Cases | Incidence rate[a] |
| 2000 | 1,596,892 | 0 | 0.000000 | 2,766,678 | 1 | 0.0000004 | 7,137,725 | 4 | 0.000001 |
| 2001 | 1,581,170 | 3 | 0.000002 | 2,788,618 | 13 | 0.000005 | 7,118,068 | 19 | 0.000003 |
| 2002 | 1,570,982 | 4 | 0.000003 | 2,799,400 | 5 | 0.000002 | 7,093,438 | 12 | 0.000002 |
| 2003 | 1,560,406 | 3 | 0.000002 | 2,791,516 | 6 | 0.000002 | 7,050,275 | 11 | 0.000002 |
| 2004 | 1,553,686 | 3 | 0.000002 | 2,786,963 | 2 | 0.000001 | 7,020,619 | 8 | 0.000001 |
| 2005 | 1,550,373 | 6 | 0.000004 | 2,783,935 | 6 | 0.000002 | 7,004,505 | 18 | 0.000003 |
| 2006 | 1,548,859 | 0 | 0.000000 | 2,778,361 | 8 | 0.000003 | 6,992,866 | 9 | 0.000001 |
| 2007 | 1,544,242 | 1 | 0.000001 | 2,765,197 | 8 | 0.000003 | 6,970,472 | 14 | 0.000002 |
| 2008 | 1,536,360 | 5 | 0.000003 | 2,754,528 | 6 | 0.000002 | 6,951,556 | 14 | 0.000002 |
| 2009 | 1,529,601 | 7 | 0.000005 | 2,744,721 | 8 | 0.000003 | 6,942,999 | 23 | 0.000003 |
| 2010 | 1,523,482 | 2 | 0.000001 | 2,739,769 | 7 | 0.000003 | 6,941,520 | 11 | 0.000002 |
| Average[b] | 1,554,187 | 3.09 | 0.0000020 | 2,772,699 | 6.36 | 0.0000023 | 7,020,368 | 13 | 0.0000019 |
| Age-adjusted Crude Incidence Rate 2000–2010 | 2.0 × 1,000,000 children/year | | | 2.3 × 1,000,0000 children/year | | | 1.9 × 1,000,0000 children/year | | |

Segregated by geographic locations for population based calculations: Maritimes: Newfounland and Labrador, Prince Edward Island, Nova Scotia and New Brunswick. BC + Yukon: British Columbia and Yukon. Prairies: Manitoba, Saskatchewan, Alberta, Northwestern Territories and Nunavut. Ontario and Quebec are reported individually

[a]Reports Crude Incidence rates

[b]Represents the average annual pediatric population (0–17 years) over a 10 year period (2000–2010) as reported by statistics Canada

Clinical signs at diagnosis included ataxia 95 (66%), hemiparesis or hemiplegia 45 (32%), hyperreflexia 57 (40%), dysmetria 49 (34.3%), and long tract signs were present in 80 (55.6%) patients. One-hundred and twelve (75.7%) children presented with cranial nerve palsies. The most common cranial nerve involvement at presentation was cranial nerve 6th palsy in 75 (53%) followed by cranial nerve 7th palsy in 74 (52%) patients.

Histological diagnosis was available for 25 (17%) patients. Thirteen patients had a biopsy at diagnosis and twelve had post-mortem examination of the tumour. Three lesions were reported to be low grade gliomas, three were

**Table 2** Clinical and therapeutic characteristics

| | *n* | % |
|---|---|---|
| **Demographics** | | |
| Age (year) | | |
| Median (range) | 6.8 | (0–17) |
| < 1 year | 4 | 2.8 |
| 1–3 year | 9 | 6.3 |
| 3–6 year | 40 | 28 |
| 6–12 year | 76 | 53.1 |
| > 12 year | 14 | 9.8 |
| Sex | | |
| Male | 71 | 49.7 |
| Female | 72 | 50.3 |
| **Clinical characteristics** | | |
| Time of symptoms | | |
| < 6 weeks | 89 | 64 |
| 6–12 weeks | 28 | 20 |
| > 12 weeks | 22 | 16 |
| Symptoms | | |
| Unstable gait | 88 | 61 |
| Abnormal eye movements | 60 | 42 |
| Headaches | 50 | 35 |
| Motor weakness | 46 | 32 |
| Vomiting | 38 | 27 |
| Signs | | |
| Cranial nerve deficits | 112 | 78 |
| Ataxia | 111 | 78 |
| Hyperreflexia | 57 | 40 |
| Dysmetria | 49 | 36 |
| Hemiplegia | 45 | 32 |
| **Treatment characteristics** | | |
| Radiation therapy | | |
| Yes | 131 | 92 |
| No | 12 | 8 |
| RT + chemotherapy | 66 | 52 |
| *On-trial chemotherapy* | *38* | *57* |
| COG-ACNS0126 | 12 | 32 |
| CPBT 1 | 10 | 26 |
| A09712:Matexafin-Gadolin | 8 | 21 |
| Carbogen + Rad | 5 | 13 |
| COG-ACNS0222 | 2 | 5 |
| POG 9836 | 1 | 3 |
| *Off-trial chemotherapy* | *28* | *48* |
| Temozolomide | 23 | 84 |
| LGG therapy | 2 | 7 |
| 99703 | 1 | 3 |
| BabyPOG | 1 | 3 |
| VP-16 | 1 | 3 |

diagnosed as embryonal not otherwise specified (NOS) (diagnosed as PNETs) and 19 as high-grade gliomas. Importantly, only seven patients with atypical radiological features underwent biopsy. (Supplementary Table 1).

## Treatment

The majority of patients 131 (92%) received upfront involved field radiation therapy. One patient diagnosed weeks after birth was treated with chemotherapy as per the Baby-POG protocol (Pediatric Oncology Group 8633/34) and three received low grade glioma protocols (Vincristine/Carboplatin or weekly Vinblastine). Eight patients received no cancer directed therapy, among those, two patients were diagnosed before 2 months of age, and five patients were toddlers with age ranging between 15 and 22 months.

Sixty-six (52%) patients received adjuvant therapies in addition to radiation. Thirty-eight patients were formally enrolled in various clinical trials as follows: Children's Oncology Group (COG)-ACNS0126 [21] (n = 12), CPBTC1 [22] (n = 10), COG-ADVL09712 [23] (n = 8), CARBOGEN + RAD [24] (n = 5), COG-ACNS0222 [25] (n = 2) and POG9836 [26] (n = 1).

Twenty-eight patients treated off trial received a variety of chemotherapy agents and additional details are provided in Table 2. Three patients received alternative cancer therapy (i.e. antineoplastons) (Table 3).

At the time of progression, three patients received radiation to new distant metastatic lesions. One patient who was not irradiated upfront received radiation at the time of progression. Forty-eight (33%) patients were treated with chemotherapy or biological treatments at the time of progression, 24 were enrolled in clinical trials with the majority, 13 (54%) enrolled in a phase II study of Nimotuzumab (NCT00600054). Seven patients were enrolled in other COG studies, and the remaining four received other experimental therapies.

## Outcomes

Progression time data were available for 131 patients. Median time to progression was 7 months (range: 0–60). Progression-free survival (PFS) at 6 and 12 months was 64% (±0.04) and 18% (±0.03), respectively.

Complete survival data were available for 140 patients. Five patients were alive at 10.1, 11, 11.2, 12 and 14.5 years after diagnosis. Out of 135 patients who died of the disease, median time to death was 10.2 months (range: 0–61). The majority of patients 112 (83%) died within 18 months of diagnosis and only 23 (17%) patients died beyond 18 months. Overall Survival (OS) at 12 and 24 months was 32% (±0.04) and 11% (±0.03), respectively (Fig. 2).

There was no significant survival advantage (PFS or OS) when comparing radiotherapy alone versus radiotherapy with adjuvant chemotherapy (Log-rank PFS p = 0.6962 and OS p = 0.1882). Clinical and radiological characteristics of patients who survived are shown in Supplementary Table 1. Importantly, three of these patients were toddlers (18, 20 and 22 months) at diagnosis. One of them had a pathological confirmation of non-histone mutant, grade III diffuse glioma. Additionally, one of these patients developed a cystic progression and pathological confirmation of low-grade glioma at the time of progression.

## Discussion

Our study describes the population of patients diagnosed with DIPG across Canada from 2000 to 2010. Over 10 years, the Canadian crude incidence rate estimated to be 1.9 cases/1,000,000 children/year, with the higher incidence rate observed in the province of Ontario with 2.3 cases/1,000,000 children/year and the lowest in the prairies with an incidence rate of 1.2 cases/1,000,000 children/year. Referral patterns to the centers in Toronto and Montreal during the study period may account for some of the higher incidence observed in these two provinces. No other predisposing risk factors were identified in the present study to account for the higher incidence in the provinces of Ontario and Quebec. Interestingly, an annual variation with peaks of incidence every 4 years were observed in our study. Although, we don't have an explanation for annual variations, it was also described in a population study from the Netherlands [27] and deserves further investigation.

Due to the overall lack of histological confirmation of DIPG, the true incidence of this condition, even in large cancer registries, is extremely difficult to estimate. The age adjusted (0–19 year) incidence rate estimates using the Surveillance, Epidemiology and End Results (SEER) database from 2000 to 2015 was 2.49 cases/1,000,000 children/year [28] representing a slightly higher incidence in the SEER population than the Canadian population. In contrast, a Dutch population-based study estimated the incidence of DIPG at 0.54 cases/1,000,000 children/year [27]. Importantly, this study described the experience in the Netherlands over a 20-year period, although, the incidence was calculated only with 55 patients diagnosed over a 6-year period and it was based on radiological diagnostic criteria, therefore, giving an explanation for the lower incidence compared to the one in our study. In contrast, the incidence reported in the SEER study is likely overestimated due to the lack of central review. The wide incidence rate range among a few studies, highlights the challenges associated with reliable epidemiology studies on DIPG.

The International Diffuse Intrinsic Pontine Glioma Registry (IDIPGR) (https://dipgregistry.org/) has made a major contribution towards understanding this challenging disease by ensuring prospective data collection. A recent IDIPGR study [29] highlighted the importance of central review and the difficulties to standardize imaging criteria for diagnosis in DIPG. Additionally, this study did not identify any associations between radiological characteristics and histone mutation status. Similarly, Chiang et al. [30] demonstrated the discrepancy between radiological findings, and histopathological diagnosis in DIPG. In our cohort, similar results were observed as six patients with classical clinical and radiological characteristics had histological confirmation of low-grade glioma (N = 3) and embryonal tumor NOS (N = 3) on histopathological examination. Our results and the recently published evidence exemplify the importance of biopsies even in patients with typical DIPG and provides a rationale to acquire tissue for histological and molecular diagnosis.

## Young patients

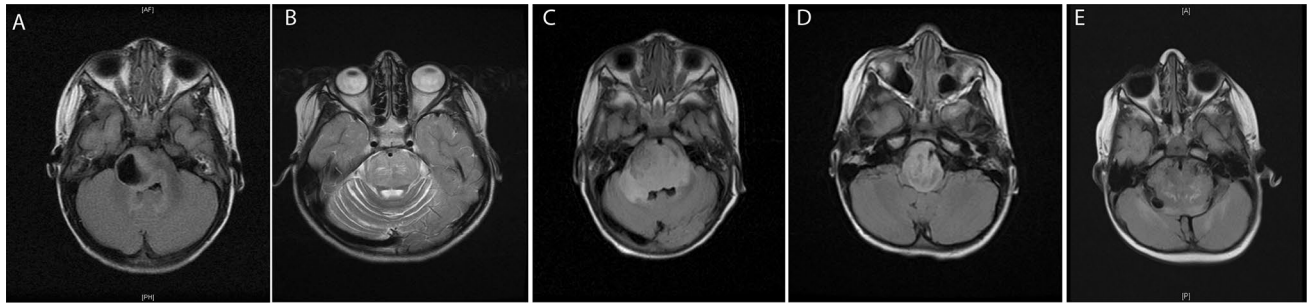
Two patients presented in the neonatal period with typical clinical and radiological features, one of them with a post-mortem histological diagnosis of what at the time was reported as "PNET". Sufit et al. [31] reported the results of gene expression analysis of seven patients meeting criteria for DIPG. Interestingly, the two younger patients in that cohort (16 and 28 months) were confirmed PNET after histological and microarray analyses. Similarly, we think these two patients correspond to the newly defined entity embryonal tumors with multilayered rosettes (ETMR) and not DIPG. Nevertheless, they were included in our study as they had typical clinical and/or radiological characteristics of DIPG and perhaps, providing a rationale to pursue biopsies in young patients with pontine tumors.

## Survivors

Five patients are long term survivors in our cohort. Three of them were diagnosed before 2-years of age. (Table 3) Broniscer et al. [32] identified age < 3 years as a predictor of better outcome in patients with DIPG. Long term survivors of DIPG have been the focus of specific reports. In a prospective clinical trial, Freeman et al. [33, 34] reported nine survivors among 130 children with brainstem glioma 5 years from diagnosis. Jackson et al. [35] reported five patients surviving 5 years beyond diagnosis among 191 treated at St Jude Children's Research Hospital. Hoffman et al. [36] reported the results from the European and International DIPG registries, showing a higher proportion of patients

**Table 3** Clinical and radiological characteristics of long-term survivors

| Sex | Age at diagnosis (Months) | Time from first presenting symptoms to diagnosis | Clinical presentation | Physical examination | Pathology | Reason for pathology | Radiation (Dose/Fractions) | Chemotherapy | Outcome | MI |
|---|---|---|---|---|---|---|---|---|---|---|
| Male | 20 | < 6 weeks | Abnormal eye movement, head tilt, motor weakness, drooling | Sixth nerve palsy, ataxia, hemiplegia, hyperreflexia, Babinsky | High Grade Glioma | Large pontine tumor with cystic/necrotic component | 54 Gy/30 | Protocol 99703 | Alive 14.5 years from diagnosis | A |
| Female | 66 | < 12–24 weeks | Unstable gait | Hyperreflexia/dysmetria, Spasticity | Not done | Not done | 54 Gy/30 | Temozolomide | Alive 11 years from diagnosis | B |
| Male | 22 | < 12–24 weeks | Difficulty swallowing/ speaking | Hyperreflexia, motor weakness | Not done | Not done | 55.8 Gy/31 | Not given | Alive 11.2 years from diagnosis | C |
| Female | 58 | > 12–24 weeks | Headache, motor weakness and facial asymmetry | Seventh nerve paly | Not done | Not done | 54 Gy/30 | ACNS0126 | Alive 10.1 years after diagnosis | D |
| Male | 18 | 6–12 weeks | Hypotonia, vomiting | Sixth and seventh cranial nerve palsy | Low Grade Glioma | Cystic progression | 54 Gy/30 at progression | Vinblastine | Alive 12 years after diagnosis | E |



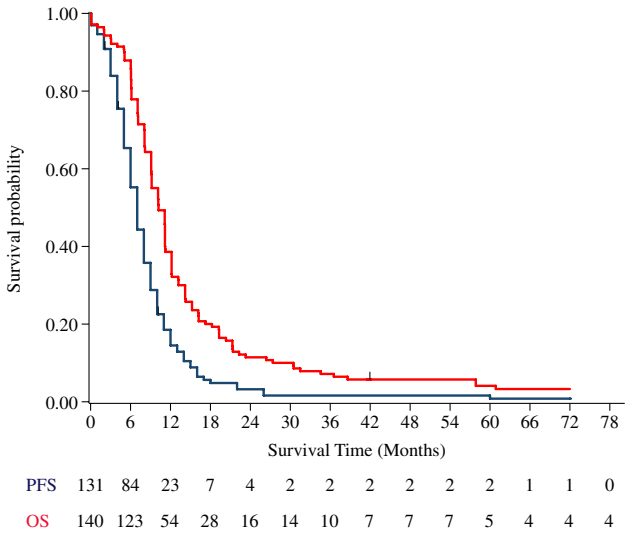



**Fig. 2** Progression-free survival (PFS) and Overall survival (OS) for the entire cohort. Blue line represents PFS, red line represents OS

younger than 3 years of age among eight very long term survivors at a median follow-up time of 6.5 years. Consistent with these reports, younger patients were overrepresented in our survivor group. Importantly, one of them had pathological confirmation of high-grade glioma and one of low-grade glioma, highlighting the biggest limitation in all the series mentioned above, as the lack of biological information characterizing the oncogenic mechanisms in this population. Importantly, these patients should no longer be included in DIPG epidemiological studies unless molecularly proven.

Lastly, this study also demonstrates that only 25% of the patients in our cohort were enrolled in a clinical trial. In a disease with such a poor outcome, one can argue, every patient would ideally be included in a clinical trial. We did not collect specific information on the reasons for this poor participation, whether it was due to a lack of open trial or the reluctance to participate in clinical trial. However, during this period 2000–2010, only six national or international studies (through COG) were open for radiologically diagnosed DIPG patients, therefore limiting access to innovative options for patients and their families. Our study is limited by the retrospective nature of the report and the small proportion of patients with histological confirmation (17%). Additionally, we could have missed a few patients if they were not referred to CPBTC centre, although this is unlikely as the CPBTC represents all paediatric oncology centers in the country.

In summary, our study highlights the challenges associated with epidemiology studies on DIPG and the need for a consensus for reporting the real incidence of DIPG as well as the urgent need to increase the availability and accessibility to clinical trials. Likewise, it emphasizes that tissue biopsies are required for accurate histological and molecular diagnosis in patients presenting with pontine lesions. This population-based study characterizes patients diagnosed with DIPG in Canada and provides instrumental information for the development of clinical trials in the Canadian population.

**Author contributions** All authors contributed in meaningful ways in the conception of the study, data acquisition, data analysis and interpretation as well as manuscript editing. All the authors agree to be accountable for all aspects of the work and approved the submitted version of the manuscript.

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**Data availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest related to this work.

**Ethics approval** This study was reviewed and approved by the ethics board of each of the participating centres.

**Informed consent** All the authors have reviewed the latest version of this manuscript and are responsible for all the work described.

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