CHAPTER 7

A twenty-year review of diagnosing and treating children with diffuse intrinsic pontine glioma in the Netherlands

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ABSTRACT

INTRODUCTION Children with diffuse intrinsic pontine glioma (DIPG) face a dismal prognosis, with a median overall survival of 9 months. Our aims are to determine the incidence of DIPG in the Netherlands and to identify points for improvement in clinical research, a prerequisite for increasing the chance to find a cure. **METHODS** We performed a population-based retrospective cohort study by evaluating all children diagnosed with DIPG in the Netherlands between 1990 and 2010. **RESULTS** The incidence of DIPG in the Netherlands corresponds with international literature. Between 1990 and 2010, a large heterogeneity of treatment schedules was applied and only a minority of patients was included in clinical trials. **DISCUSSION** Given the rarity of DIPG, we emphasize the need for (inter-)national trials to facilitate the identification of potentially effective therapeutics in the future. This can be supported by the recent development of a European DIPG registry enabling international study collaborations.

INTRODUCTION

Diffuse intrinsic pontine glioma (DIPG) is a rare and childhood-specific malignancy of the brainstem. Children with DIPG face a dismal prognosis, with a median overall survival (MOS) of 9 months [1]. Over the years, DIPG has been distinguished from other brainstem entities by numerous classification systems, using criteria based on location, growth pattern, size, and histopathological grade [2–4]. It was, however, not until the 1990s that DIPG was classified separately from more focally growing tumors, and showed to have its specific, dismal prognosis [5]. Most epidemiological data about DIPG come from America and Canada. It is estimated that gliomas arising in the brainstem account for 10–20% of pediatric CNS tumors and that 80% of these can be classified as a typical DIPG [6]. There is, however, a lack of epidemiological data from European countries.

Although better and more uniform classification criteria were developed, none of the applied treatment options so far has yielded a substantial survival benefit in patients suffering from a typical DIPG [7]. Radiotherapy remains the only effective, albeit palliative, treatment option, with a few months survival increase compared to best supportive care and a transient improvement of clinical performance and quality of life [8,9].

We evaluated the 20-year history of diagnosing and treating patients with DIPG in the Netherlands, to gain more insight in the epidemiology and current treatment approach. The main purpose of this study is to determine the incidence of DIPG, in a country which is representative of Western Europe. In addition, we will evaluate the applied treatments, including the application of clinical trials. With this, we aim to find possible points for improvement in clinical research into this rare disease.

METHODS

This study was approved by the institutional review board of VU University Medical Center (VUmc, Amsterdam, The Netherlands) and the scientific committee of the Dutch Childhood Oncology Group (DCOG).

Identification of study cohort

A search was performed in the Pathological Anatomy National Automated Archive, the databases of the centers of the DCOG and pediatric radiotherapy centers, a total of eight academic university medical centers and one regional hospital. To ensure the inclusion of typical DIPG patients, we solely evaluated patients of whom MR images from time of

diagnosis could be obtained for central review. In this central review, DIPG was defined as a T1-weighted hypointense and T2-weighted hyperintense tumor with at least 50% involvement of the pons on T2 [5]. Histological determination was not required for this study. If, however, a biopsy was performed and pathology data could be retrieved, than the data were analyzed. We did not exclude patients on the basis of their duration of symptoms before diagnosis, since this criterion was not well documented and not systematically used to define DIPG during our study period. However, since nowadays a longer symptom duration is assumed to be atypical for DIPG patients [1], we did perform additional analyses on patients with a symptom duration of more than 6 months.

Data collection

Demographics and clinical data were obtained from the patient records. The presence and duration of cranial nerve deficits, long tract symptoms and ataxia were scored when available. MR images were centrally reviewed. Information from pathology reports was retrieved (i.e., biopsy or autopsy). Data on treatment strategies (surgery, chemo- and radiotherapy) and participation in clinical trials, both at time of diagnosis and at time of disease progression, were collected. Unfortunately, we could not in all cases retrieve the exact nature of (clinical and/or radiological) responses to (first or subsequent) treatments and could therefore not describe the exact pattern of progression (i.e., local and/or metastatic). Progressive disease (yes or no) was defined as clinical signs of disease progression (i.e., increase of symptoms or new symptoms) and/or radiological tumor progression, obtained from the patient records and radiology reports.

Statistics

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA: released 2011). Patient data regarding demographics, diagnosis and treatment schedules were analyzed by descriptive statistical methods. The incidence of DIPG was calculated for the period between 2004 and 2009, these being the most reliable years in terms of complete registration. Survival analysis was performed by Kaplan-Meier estimates.

RESULTS

Patient population

The search resulted in a list of 207 patients diagnosed with a brainstem tumor between 1990 and 2010 in the Netherlands, illustrated in Figure 1. We excluded patients with non-glioma lesions (n = 11) and patients diagnosed with neurofibromatosis (n = 7).

Based on the current classification of a typical DIPG, we also excluded patients with pilocytic astrocytoma (WHO grade I; n = 3), or with dorsally exophytic tumors and tumors occurring elsewhere in the brainstem, that is, mesencephalic or medullary tumors (n = 29). Out of 207 patients diagnosed with a brainstem tumor, 157 patients were therewith identified as having a PG. In 117 cases (75%), MR images were available for central review, of which 88% of patients were classified as having a typical DIPG (n = 103). Further analyses concerning the applied treatment approach were performed in this cohort of 103 MRI-confirmed typical DIPG patients.

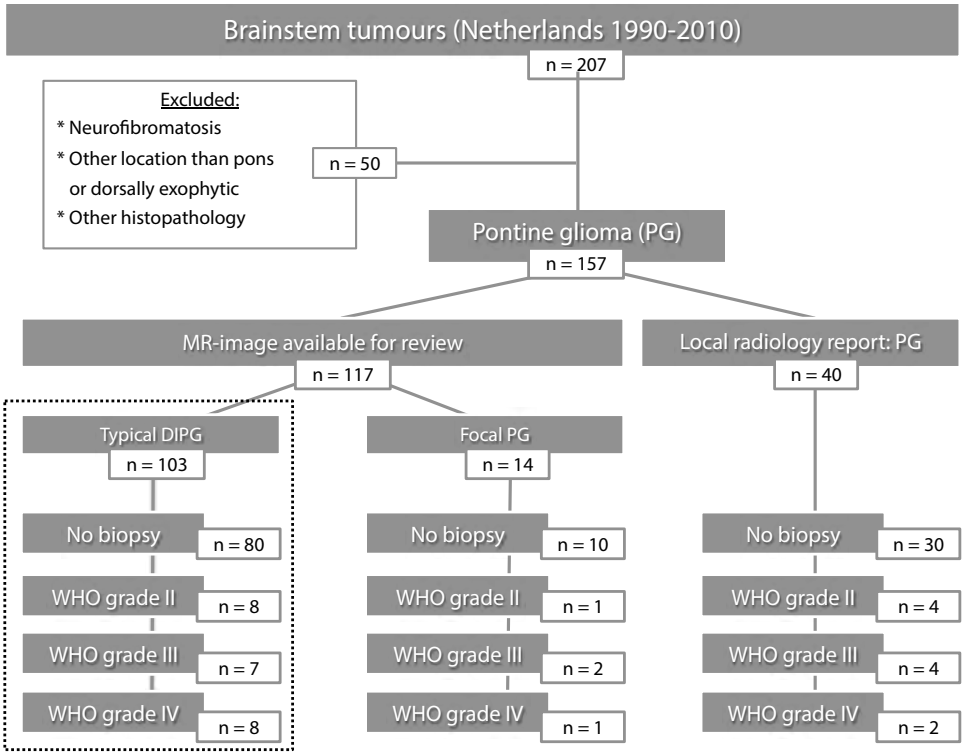

FIGURE 1 | Overview of patients diagnosed with diffuse intrinsic pontine glioma in the Netherlands (1990–2010).

The dotted square indicates the evaluated population in this retrospective study.

Incidence

We could not retrieve all MRIs from patients diagnosed before 2004, whereas for the time period from 2004 to 2009, MRI scans from all patients could be collected and centrally reviewed. Therefore, this time period was used to ascertain the incidence of

DIPG. In 6 years' time, 55 patients were diagnosed as having a typical DIPG and 9 as having a focal PG. The incidence of DIPG in the Netherlands was therefore estimated to be nine patients per year (0.54 per 1,000,000; 2.32 per 1,000,000 aged 0–20 years). However, annual variations were observed (range 5–13 per year). No seasonal variations were observed.

Distribution of patients in the Netherlands

The 103 DIPG patients were diagnosed and/or treated in nine hospitals distributed throughout the Netherlands. These hospitals are all the possible sites where DIPG patients can be referred to within our boarders. The number of patients per center over the course of 20 years ranged from 1 to 26 (median 10).

Demographics

The mean age of patients was 7.2 years (standard deviation 3.4). There was a balanced gender distribution (boys n = 49, girls n = 54).

History & physical examination

From 96% of patients (99/103), information on the duration of symptoms before diagnosis could be retrieved from the patient records. The median duration of symptoms before diagnosis was 1.0 month (range 0–16 months). The exclusion of six patients with a symptom onset duration of more than 6 months did not influence the median duration of 1 month (range 0–5 months). Neurological examination at the time of initial diagnosis showed cranial nerve deficits to be present in 98 patients (95%), long-tract symptoms in 78 (76%) and ataxia in 78 patients (76%).

Diagnosis

In each hospital, the original diagnosis was made based on MR imaging. In 23 patients (22%), MRI of the brain was supplemented with an MRI of the spine. None of the local radiology reports at time of diagnosis described neuraxis metastases. In 23 children (22%), imaging was supplemented with pathology (Fig. 1), showing WHO grade II, III and IV astrocytomas. Additional analyses of the six patients with a symptom duration of more than 6 months, showed typical DIPG images on MR in all patients. In one of these six cases a biopsy was performed, showing astrocytoma grade II. In further analyses concerning the applied treatment approach, these six patients were therefore not separated from the other patients.

Therapy at initial diagnosis

At the time of initial diagnosis, 89 out of 103 DIPG patients (86%) received anti-tumor treatment (Fig. 2). When only supportive care was applied (n = 14; 14%), this was either due to very young age of the child (n = 2), poor neurological state (n = 4), parental refusal (n = 3) or parental preference for alternative medicine or supportive care only (dexamethasone) (n = 5). Reports on dexamethasone schedules were incomplete and could therefore not be analyzed.

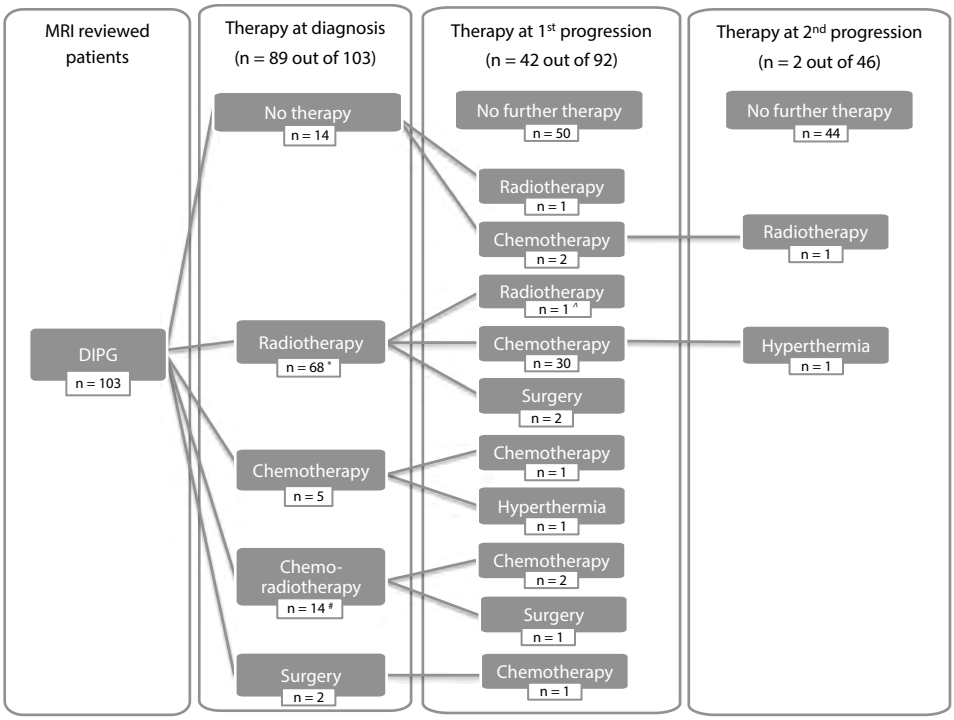

FIGURE 2 | Treatment schedules applied to diffuse intrinsic pontine glioma patients in the Netherlands (1990–2010).

*Includes one patient who received radiotherapy together with homeopathic Ruta-6 and calcium phosphate. #Includes one patient who stopped radiotherapy after the second day of treatment because of neurologic deterioration. The patient continued with temozolomide instead. ^Includes one patient who received spinal irradiation after initial radiotherapy treatment because of leptomeningeal metastasis.

Of the 89 treated patients at time of diagnosis, a total of 82 patients (92%) received radiotherapy, of which the majority (n = 68; 83%) received radiotherapy only. One of these patients received concomitant homeopathic Ruta-6 and calcium phosphate. A total of 19 treated patients (21%) received some form of chemotherapy, either combined with radiotherapy (n = 14) or as single therapy (n = 5). The most widely prescribed

chemotherapeutic agents at the time of diagnosis were temozolomide and vincristine/carboplatin (Table 1). Four patients (7%) underwent a partial resection of their tumor together with initial therapy *(not shown)*, whereas two patients (2%) underwent surgery only, which consisted of a partial resection combined with the placement of an extra ventricular drain (Fig. 2).

Therapy at disease progression

In 11 cases, data on progressive disease and therapy were not available for evaluation. In all 92 evaluable DIPG patients, progressive disease was reported after an initial response to therapy. Forty-two of these evaluable patients (46%) received second-line treatment (Fig. 2). The majority, 36 patients (39%) were treated with chemotherapy, which mainly consisted of temozolomide (Table 1). Three of these patients received a second chemotherapy regimen, which in all cases differed (i.e., in drugs or doses) from the regimen at time of diagnosis. Irradiation at time of disease progression was performed in two patients (2%), but these patients were not radiated at time of diagnosis. One patient receiving second-line therapy underwent a partial resection of the tumor prior to chemotherapy *(not shown)* and three patients (3%) underwent a partial resection of tumor tissue as single therapy at time of disease progression (Fig. 2). In all cases, this was the first surgical intervention. In one patient, an alternative treatment strategy, hyperthermia, was applied at the time of progressive disease.

In 46 patients (50%), a second episode of disease progression was reported (Fig. 2) after a period of stable disease. At this point, the majority of these patients (n = 44; 96%) received no further therapy and palliative care was initiated. Two patients (4%) with secondary progressive disease received third-line therapy: one patient, who did not receive radiotherapy before, was irradiated and the other patient received alternative therapy (hyperthermia) (Fig. 2).

Uniformity of applied treatments

Radiotherapy was applied to a total of 85 out of 103 patients (83%) at some point during their disease course. Table 2 shows the radiotherapy schedules that were applied at the time of diagnosis and at the time of progression. Radiotherapy was applied in each of the treatment centers.

Table 1 shows the various chemotherapeutic regimens that were applied at initial diagnosis and at time of progressive disease. Chemotherapy at the time of diagnosis was applied in six hospitals (with n = 9, n = 5 and n = 2 in three hospitals, and n = 1 in the remaining hospitals). Chemotherapy at the time of progressive disease was applied

TABLE 1 | Chemotherapeutic agents and schedules.

Chemotherapeutic agents	At diagnosis (n)	At progressive disease (n)
Temozolomide (*inter alia TMZ study - www.trialregister.nl - NTR227*) [12]	5	30
Temozolomide & thalidomide & erlotinib	-	1
Temozolomide & imatinib & dichloroacetate	-	1
Vincristine & procarbazine& methotrexate & dexamethasone followed by vincristine & lomustine	1	-
Vincristine & lomustine	1	-
Vincristine & cyclophosphamide followed by carboplatin & procarbazine and etoposide & cisplatin	1	1
Vincristine & carboplatin followed by temozolomide	3	-
Vincristine & carboplatin	1	1
Vincristine & carboplatin followed by temozolomide & lomustine	1	-
Gemcitabine followed by high dose chemo with stem cell reinfusion and irinotecan & bevacizumab & erlotinib (& everolimus) (*VUmc DIPG 01 study - www.trialregister.nl - NTR2391*) [13]	2	-
Etoposide (& carboplatin)	2	2
Cisplatin	2 +	- +
Patients receiving chemotherapy treatment	19	36

n: Number of patients

TABLE 2 | Radiotherapy schedules.

Schedule	Total Gy	n
13 x 3.0	39.0	15
16 x 2.8	44.8	12
15 x 3.0	45.0	3
Unknown	49.4	1
25 x 2.0	50.0	1
28 x 1.8	50.4	6
30 x 1.8	54.0	16
31 x 1.8	55.8	1
32 x 1.75	56.0	1
32 x 1.8	57.6	1
33 x 1.8	59.4	8
Hyperfractionated	70.2	2
Other	-	18 +
Patients receiving RT treatment		85

Gy: Gray; n: Number of patients; RT: Radiotherapy

in eight hospitals (with n = 5 in two hospitals, n = 2 in two, n = 1 in two and n = 3 and n = 17 in the remaining hospitals). As with radiotherapy, no general guidelines were available or used. The majority of patients was treated off-trial with temozolomide, mainly at progression of disease. Reports on dosage and schedules were incomplete and could therefore not be further analyzed.

Clinical trials

Over the course of our study period, 19 patients (18%) of all children diagnosed with DIPG in the Netherlands were enrolled into a prospective clinical trial. Only trials that were approved by an institutional review board, the scientific committee of the DCOG, and trials that were included in a trial registry, were evaluated. The Childhood Oncology Group ACNS-0126 study, a multicenter, Phase II prospective cohort study was initiated in 2002, exploring the toxicity and efficacy of temozolomide as adjuvant therapy [10,11] in pediatric high-grade glioma and DIPG. One center in the Netherlands participated in this study. From January 2004, patients with recurrent or progressive PNET or high-grade glioma (including DIPG) could be included in a similar Phase II study exploring the use of temozolomide [12]. Both studies have been closed for accrual. In 2010, a single-center study was opened, which offers a broad and at the same time targeted approach of DIPG. Therapy consists of standard radiotherapy (54 Gy) combined with gemcitabine as radiosensitizer at diagnosis. At disease progression, therapy consists of a backbone of irinotecan and bevacizumab combined with escalating doses of erlotinib and everolimus. This is the first study in the Netherlands that offers the option of undergoing a biopsy. A biopsy, however, is not mandatory for enrolment [13]. This study is still accruing patients.

Survival

In the total cohort of MRI-confirmed typical DIPG patients, the progression-free survival (PFS) was 6 months and the MOS was 9.5 months (Fig. 3 & Table 3). Children <3 years of age showed a relatively short PFS of 4.0 months and a relatively long MOS of 11.0 months (log-rank p = 0.028 and 0.015, respectively). For the children aged 9–18 years, no longer PFS or MOS was observed (log-rank p = 0.595 and 0.868, respectively).

Table 3 shows the result of additional analysis of the separate treatment groups at time of diagnosis. We could not perform specific analyses per treatment schedule, drug or dosage due to low patient numbers.

In this large, unselected, nationwide population-based cohort, six patients (6%) with a typical DIPG on MRI were classified as long-term survivors. Long-term survival was

defined as having a survival from initial diagnosis beyond 24 months (Fig. 3). The PFS of these patients was 42 months and the MOS 46 months, with three patients being alive at 27, 79 and 161 months, respectively (Table 3; log-rank p = 0.000 and 0.000, respectively).

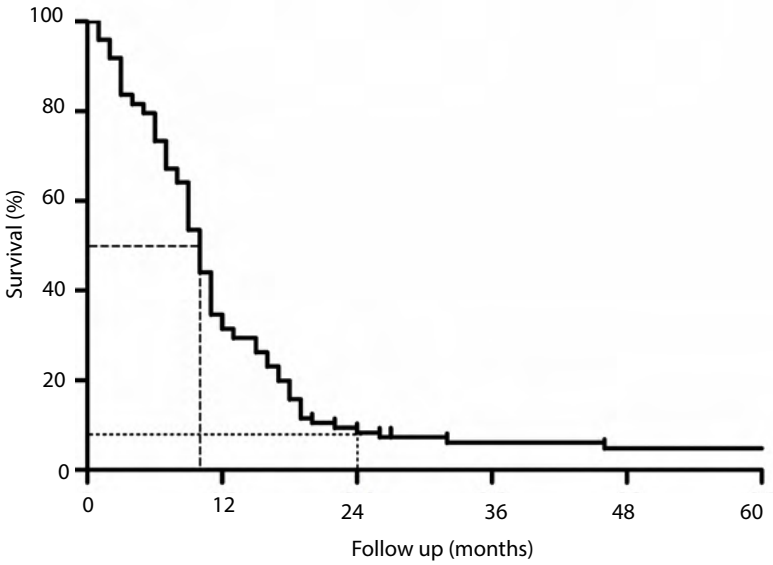

FIGURE 3 | Survival of diffuse intrinsic pontine glioma patients in the Netherlands (1990–2010).
The dashed line indicates a median overall survival of 9.5 months. The dotted line indicates a 2-year survival of 6%.

TABLE 3 | Survival analysis of treatment groups at time of diagnosis. †This group is too small to analyse (n = 2).

Group	**PFS**	**95% CI**	**MOS**	**95% CI**
Overall (n = 103)	6.0	4.8 - 7.2	9.5	8.7 - 10.3
Age <3 years (n = 8)	4.0	0.0 - 13.7	11.0	0.0 - 27.6
Age 9-18 years (n = 24)	5.0	1.1 - 8.9	9.0	7.4 - 10.6
LTS (n = 6)	42.0	2.8 - 81.2	46.0	16.8 - 75.2
Therapy group (at diagnosis)	**PFS**	**95% CI**	**MOS**	**95% CI**
No therapy	--	--	3.0	0.0 - 6.3
Radiotherapy	6.0	4.2 - 7.6	10.0	8.9 - 11.1
Chemotherapy	5.0	0.0 - 15.7	10.0	1.4 - 18.6
Chemo-radiotherapy	8.0	4.6 - 11.4	9.0	8.2 - 9.8
Surgery†	--	--	--	--

LTS: Long-term survival (>24 months); MOS: Median overall survival; PFS: Progression-free survival

DISCUSSION

We determined the population-based, and MRI-confirmed, incidence of patients diagnosed with DIPG in the Netherlands, and showed how these patients were treated over the past 20 years. Each year, on average, nine patients with typical DIPG are diagnosed, equally distributed geographically throughout the Netherlands, without an indication for seasonal variations. The incidence of 2.32 per 1,000,000 individuals aged 0–20 years corresponds to international data from the USA [14].

It is noteworthy that the limited number of patients was diagnosed and/or treated in nine different hospitals, resulting in very low patient numbers per hospital. More importantly, only a minority of patients (18%) was enrolled into a prospective clinical trial, although during our study period three clinical trials were available for patient inclusion. Only the first study, which was an international collaboration initiated by the Children's Oncology Group comprising 230 study locations, was successfully completed [11]. The second study was a Dutch multicenter study. This study, however, was discontinued and the results are yet to be published. The third study is a single-center study, which is still open of accrual, but with an inclusion rate of only one patient (11%) per year on average.

This retrospective study shows that DIPG patients are mainly treated according to single-center guidelines and even individualized therapy. There are still no strict national guidelines for both radio- and chemotherapy, resulting in a heterogeneous application of treatment schedules. More importantly, DIPG patients are often not included in clinical trials. This could lead to selection bias when a limited number, or a selected group of patients, participate in clinical trials. Further research is needed to investigate why patients are mainly treated off-study. In view of the rarity of the disease, this heterogeneity might be caused by the limited number of patients treated per center, with a median of 10 patients over the course of 20 years. A rare disease such as DIPG might benefit from centralization in a limited number of specialized hospitals, in this case pediatric cancer centers [15], together with (inter)national consensus on the approach of these patients and optional inclusion in collaborative clinical trials [1,7].

In addition to co-operation in existing clinical trials, we emphasize the need for collaboration in other fields of DIPG research, like biological studies and molecular drug imaging using PET. Between 1990 and 2010, 78% of patients did not undergo a biopsy in addition to radiological diagnoses, and 98% of patients did not get the chance to participate in an autopsy study. From the introduction of offering biopsies in the VUmc DIPG 01 study and the opening of the autopsy study [16], this is increasingly performed. However, in view of the low incidence of DIPG in the Netherlands, international collaboration is urgently needed. This is underlined by the fact that DIPG biopsy and

autopsy studies have advanced the understanding of the disease, with the discovery of a K27M mutation in H3.3 or H3.1, perturbations in genes of the receptor tyrosine kinase/Ras/PI3K signaling pathway and the overexpression of VEGF, which provides useful information for drug development, design of novel therapies and possibly treatment stratification [17–19]. Future international studies comparing biopsy and autopsy material will also reveal more about the biological changes, either due to the natural course of the disease, or influenced by therapy. In addition, emerging PET studies will reveal more about the *in vivo* behavior of drugs, such as blood-brain barrier passage and tumor pharmacokinetics [20]. Collaborative international biological and diagnostic studies will thus contribute to the discovery of novel therapies for future clinical trials.

Our complete cohort of 103 MRI-confirmed DIPG patients showed a PFS of 6 months and a MOS of 9.5 months, with a significant longer survival time in children less than 3 years of age. The relatively short PFS in this age group is possibly due to the fact that these children did not receive radiotherapy. These data, as well as the data from the subgroups of patients receiving radiotherapy alone, or radiotherapy combined with chemotherapy, are in accordance with previously published data [1,7,21,22]. The relatively long MOS of the patients receiving chemotherapy only is probably due to confounding bias based on the relative young age of patients in this group. Other studies have reported longer survival times for children aged 9–18 years, however, this could not be confirmed in our cohort of patients [23]. Our cohort harbored a total of six, relatively young, long-term survivors, which is in agreement with international literature [24]. Further research is needed to better understand this intriguing group of DIPG patients, which might have a distinct survival based on specific biological features.

With this nationwide, population-based retrospective cohort study, we confirm the assumed low incidence of DIPG and show that a poor accrual of DIPG patients in clinical trials results in a lack of comprehensive data on demographics, history, physical examination, diagnosis (both imaging and biology), outcome, but most importantly effectiveness per treatment schedule, drug or dosage. Given the rarity of DIPG, we emphasize the need for (inter-)national data and trials to facilitate the identification of potentially effective therapeutics in the future. This can be supported by the recently developed European DIPG registry [25] by the DIPG network of the International Society of Pediatric Oncology Europe. The International Society of Pediatric Oncology Europe DIPG registry was developed in parallel with that in the USA [26]. The first large-scale international study that will be performed in the setting of the European DIPG registry will be an evaluation of all European long-term survivors.

EXPERT COMMENTARY

In view of the very poor prognosis for children with DIPG, patients should be able to participate in clinical trials. Given the rarity of DIPG, we emphasize the need for (inter-) national collaboration and trials to facilitate the identification of potentially effective therapeutics in the future. This can be supported by the recent development of a European DIPG registry.

FIVE-YEAR VIEW

Given the rarity of DIPG and lack of comprehensive data from large unselected cohorts of DIPG patients, we envision that the European DIPG registry will contribute to future clinical research. A comprehensive database will for instance facilitate studies on subgroups of DIPG, the analysis of long-term survival and the evaluation of decision-making. The database will also function as a control cohort for (inter)national clinical trials without randomization, which is most useful in a rare disease such as DIPG.

KEY ISSUES

- Patients with diffuse intrinsic pontine glioma (DIPG) face a dismal prognosis, with a median overall survival of 9 months.
- In recent decades, the survival has not improved despite several treatment strategies that have been explored.
- The incidence of DIPG in the Netherlands is 9 (5–13) patients per year (0.54 per 1,000,000; 2.32 per 1,000,000 aged 0–20 years).
- Between 1990 and 2010, for both radio- and chemotherapy, more than 10 different schedules or agents were used.
- In this period, only 18% of patients were formally included in clinical trials.
- Poor accrual of DIPG patients in clinical trials results in a lack of comprehensive data on demographics, history, physical examination, diagnosis (both imaging and biology), outcome, but most importantly effectiveness per treatment schedule, drug or dosage.
- Given the rarity of DIPG, we emphasize the need for (inter-)national trials to facilitate the identification of potentially effective therapeutics in the future.
- Recently, a European DIPG registry [25] has been developed by the DIPG network of the International Society of Pediatric Oncology Europe. This registry will enable the evaluation and follow-up of clinical and centrally reviewed radiology data of all European patients with DIPG, both in- and outside clinical trials, which will give a realistic picture of the actual spectrum of DIPG patients. Subsequently, a comprehensive European DIPG registry will pave the way for further international collaborations and, hopefully, European clinical DIPG trials.

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