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Predictors of mortality and tumor recurrence in desmoplastic infantile ganglioglioma and astrocytoma—and individual participant data meta-analysis (IPDMA)

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Abstract

Purpose—Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) are classified together as grade I neuronal and mixed neuronal-glial tumor of the central

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Author contributions SW, AF and ACW designed the systematic review; SW, MZS, and ACW performed the literature review and created the IPDMA; SW, AGW, GMI and ACW designed and performed the analysis the data; SW, MZS, and ACW drafted and revised the manuscript; IJA, AF, CE, SESL, BLC, CML, JMO, JRG, RGE, JGO, and ACW critically reviewed the literature, supervised the scientific analysis, and evaluated the significance of the findings.

Conflict of interest The authors report no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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nervous system by the World Health Organization (WHO). These tumors are rare and have not been well characterized in terms of clinical outcomes. We aimed to identify clinical predictors of mortality and tumor recurrence/progression by performing an individual patient data meta-analysis (IPDMA) of the literature.

Methods—A systematic literature review from 1970 to 2020 was performed, and individualized clinical data for patients diagnosed with DIA/DIG were extracted. Aggregated data were excluded from collection. Outcome measures of interest were mortality and tumor recurrence/progression, as well as time-to-event (TTE) for each of these. Participants without information on these outcome measures were excluded. Cox regression survival analyses were performed to determine predictors of mortality and tumor recurrence / progression.

Results—We identified 98 articles and extracted individual patient data from 188 patients. The cohort consisted of 58.9% males with a median age of 7 months. The majority (68.1%) were DIGs, while 24.5% were DIAs and 7.5% were non-specific desmoplastic infantile tumors; DIAs presented more commonly in deep locations ($p = 0.001$), with leptomeningeal metastasis ($p = 0.001$), and was associated with decreased probability of gross total resection (GTR; $p = 0.001$). Gender, age, and tumor pathology were not statistically significant predictors of either mortality or tumor recurrence/progression. On multivariate survival analysis, GTR was a predictor of survival (HR = 0.058; $p = 0.007$) while leptomeningeal metastasis at presentation was a predictor of mortality (HR = 3.27; $p = 0.025$). Deep tumor location (HR = 2.93; $p = 0.001$) and chemotherapy administration (HR = 2.02; $p = 0.017$) were associated with tumor recurrence/progression.

Conclusion—Our IPDMA of DIA/DIG cases reported in the literature revealed that GTR was a predictor of survival while leptomeningeal metastasis at presentation was associated with mortality. Deep tumor location and chemotherapy were associated with tumor recurrence / progression.

Keywords

Astrocytoma; BRAF; Desmoplastic; Infantile; Ganglioglioma

Introduction

The World Health Organization (WHO) classification of central nervous system (CNS) neoplasms categorizes desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) together as a single diagnosis, among grade I entities under the “neuronal and mixed neuronal-glial” heading [1]. Though these low grade tumors are generally associated with a favorable prognosis, some tumors have malignant features and demonstrate spontaneous recurrence [2]. As an extremely rare tumor that typically arises in infancy, our collective understanding of the biology of this disease has largely been derived from case reports or small case series. Mallucci et al. have proposed that it may not be sufficient to manage these tumors with surgery alone, for which gross total resection (GTR) was the goal [3]. Due to recurrence in a subset of these tumors, as well as the potential for malignant transformation, postsurgical surveillance is necessary, and chemotherapy and/or radiation may be used as adjuvant treatment upon recurrence [4]. However, there’s a lack of data on the role of adjuvant therapy in DIA/DIG.

We and others have previously found that aggressive molecular and histopathological features were actually quite common among DIA and DIGs, though such highgrade characteristics did not correlate with worse clinical outcomes, regardless of location [5–7]. Specifically, we have recently reported that DIA/DIG were frequently associated with BRAF mutations [7]. In order to better understand the biology and pathology of these tumors, we aimed to identify clinical predictors of survival and tumor progression, as well as the role of adjuvant therapy,by performing an individual patient data meta-analysis (IPDMA) of an exhaustive search of the existing literature for cases of both infantile and non-infantile DIA/DIG [7–9]. To our knowledge, this study is the first study presenting survival analysis data using an IPDMA approach for DIA/DIG.

Methods

Individual participant data meta-analysis

We performed a comprehensive literature search using Pubmed and Google Scholar to identify publications containing individual cases of DIA and DIG. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol was used to identify studies in the English language published between Jan 1970 and July 2020. Keywords used to search included “desmoplastic”, “infantile”, “non-infantile”, “ganglioglioma”, “astrocytoma”, “desmoplastic infantile ganglioglioma”, “desmoplastic cerebral astrocytoma of infancy”, “desmoplastic infantile tumor”, “desmoplastic non-infantile ganglioglioma”, “dysembryoplastic neuroepithelial tumor”, and “desmoplastic supratentorial neuroepithelial tumors of infancy”, “desmoplastic astrocytoma”, and “desmoplastic ganglioglioma”. Studies were manually screened for duplicates and non-English language publication, as well as for any inclusion availability of individualized patient data, by 2 independent reviewers. When possible, authors of studies containing only aggregated data were contacted to assess the availability of individualized data for collection. However, if individualized patient data was not available, aggregated studies were not included in this IPDMA. Outcome measures of interest were mortality and tumor recurrence/progression, as well as the time-to-event (TTE) for each of these. Participants without information on 1 or both these outcome measures were excluded. Missing data were treated as “not applicable” in statistical analyses.

Statistical analysis

Continuous variables were reported as means, standard deviations (SD), medians, and interquartile ranges (IQR). Categorical variables were reported as frequencies and percentages. Pearson’s Chi Square Test for Independence was utilized to assess the relationship between categorical variables, and Student’s t-test was utilized for comparison of means/distributions of continuous variables. Cox Regression was utilized to determine the effect of patient gender, age, pathology, extent of resection (EOR), presence of distant leptomeningeal metastasis at the time of presentation, deep tumor location, *BRAF* mutation, radiation therapy and chemotherapy, on both mortality and tumor recurrence/progression. We report findings using hazard ratios (HR), 95% confidence intervals (CI) and p-values. A multivariate Cox Regression survival analysis was performed on variables with a p value < 0.2 on univariate analysis to identify independent predictors of outcome. All

statistical analyses were performed using Stata15 (College Station, TX: StataCorp LP) using a significance value of $\alpha = 0.05$.

Results

Patient demographics and clinical characteristics

Using PRISMA guidelines, we obtained individual patient data in 106 articles with a total of 305 patients in the literature with desmoplastic tumors of various pathology (Fig. 1). Of this cohort, 98 articles with a total of 188 patients contained individual patient outcome variables of interest and were eligible to be included in this for this IPDMA. The individual studies, in addition to the number of individual patients and their variables, are available online (Supplemental Table 1). The articles were published between 1978 and 2020, and were single case reports or smaller case series containing between 1 and 12 patient cases per study.

Patient demographics

The demographic and characteristics of the 188 patients included in the IPDMA are displayed in Table 1. Information on patient gender was available on 185 patients. The cohort consisted of 58.9% males, with a male:female ratio of 1.43. The mean age at presentation was 27.5 months, while the median age was 7 months (IQR 4–14 months; Fig. 2). All except 1 patient were children ≤ 18 years of age, and the majority (80.3%) were infants ≤ 2 years of age.

Tumor location and pathology, and molecular biology

In this IPDMA, desmoplastic tumors were categorized into 3 groups by histopathology (Table 1). Group 1 consisted of DIG and desmoplastic non-infantile ganglioglioma (DNIG), and contained 128 (68.1%) patients. Group 2 consisted of DIA, desmoplastic cerebral astrocytoma of infancy (DCAI), superficial cerebral astrocytoma of infancy (SCAI) and superficial cerebral astrocytoma attached to dura (SCAAD) pathologies. There were 46 patients (24.5%) individuals in group 2. Group 3 consisted of those cases in which the distinction between glial and glio-neuronal histology was not made, including desmoplastic infantile tumor (DIT), desmoplastic neuroepithelial tumor (DNT), and desmoplastic supratentorial neuroepithelial tumors of infancy (DSNT); a total of 14 patients (7.5%) fell into this group. There was no statistical difference in the age at diagnosis amongst these 3 groups ($p = 0.71$). However, DIAs presented more commonly in deep locations compared to DIGs (36.6% vs. 13.0%; $\chi^2 = 10.5$; $p = 0.001$). DIAs also presented more frequently with leptomeningeal metastasis (26.8% vs. 7.4%; $\chi^2 = 11.3$; $p = 0.001$) and were associated with decreased probability of GTR (32.6% vs. 60.9%; $\chi^2 = 10.9$; $p = 0.001$).

Information on tumor location was available in 163 cases. Although most patients had superficial lobar lesions, 30 patients (18.4%) harbored deep seated tumors located in the tentorial, posterior fossa, intraventricular, thalamic, hypothalamic, and sellar regions. Leptomeningeal metastases at the time of diagnosis, either defined by the authors or involving synchronous or metachronous lesions in multiple areas or the brain or the spine, were present in 20/171 patients (11.7%) for whom information was available.

Genetic studies were performed and reported for 55 patients (29.3% of cohort), and a *BRAF* mutation was reported in 18/55 patients (32.7%). This included 12 cases of BRAF V600E, 4 cases of BRAF V600D, 1 case of BRAF V600delinsDL, and 1 case of BRAF V600_W604delinsDQTDG mutation. Interestingly, 6 patients with *BRAF* mutations were found in DIA cases for whom genetic studies were available (42.9%), while 12 *BRAF* mutations were found in the DIG population tested (29.3%), although this did not reach significance ($\chi^2 = 0.9$; $p = 0.35$). Other mutations included CDKN2A promotor hypermethylation, 8p22-pter loss, 13q21 gain, ALK-EML4 fusion, TP53, NF1, FGFR3, and ATRX mutations.

Malignant transformation

In this group, there were 9 patients (5.0%) with reported malignant transformation, most frequently to glioblastoma multiforme (GBM), over a mean period of 4.2 ± 3.6 years. The data is extremely limited; however, malignant transformation was not associated with older age ($p = 0.36$), DIA tumor pathology ($\chi^2 = 0.4$; $p = 0.51$), deep tumor location ($\chi^2 = 0.2$; $p = 0.62$), or leptomeningeal metastasis at presentation ($\chi^2 = 0.008$; $p = 0.93$).

Treatment

In this cohort, information on surgical management was available in 171 patients. The majority of the cohort (103 patients, 60.2%) underwent gross total resection (GTR) of the lesion, while 58 patients (33.9%) underwent subtotal resection (STR), and 9 patients (5.3%) underwent biopsy. One patient (0.6%) underwent no surgical intervention; the pathology was determined on autopsy. A small proportion of the cohort (43 patients, 22.9%) underwent adjuvant therapy, either in lieu of surgery or following surgical resection. Thirty-two patients (17.0%), with a median age of 5 months (IQR 3–8 months), underwent chemotherapy, while 18 patients (9.6%), with a median age of 6 months (IQR 3–24 months), underwent radiation. There were no statistically significant differences in age or underlying pathology between patients who underwent adjuvant therapy, and those who did not. Predictably, patients who harbored deep lesions ($\chi^2 = 10.4$; $p = 0.001$) were statistically more likely to undergo chemoradiation. Although a small cohort of patients with GTR underwent chemotherapy ($n = 7$) and radiation ($n = 6$), achievement of GTR was negatively correlated with chemoradiation administration ($\chi^2 = 25.1$; $p < 0.001$) Patients who had leptomeningeal metastasis at presentation ($\chi^2 = 7.9$; $p = 0.005$) and who experienced malignant transformation ($\chi^2 = 9.9$; $p = 0.002$) had greater probability of undergoing chemotherapy, but not radiation.

Survival analysis

A Cox regression survival analysis was performed to identify the predictors of mortality (Table 2). Median follow-up time was 2 years (IQR 1–5.5 years), during which the cohort mortality was 8.6%. Univariate survival analysis demonstrated that leptomeningeal metastasis at presentation (HR 7.8; 95% CI 2.8–21.8; $p < 0.001$) and deep tumor location (HR 7.9; 95% CI 2.6–24.2; $p < 0.001$) were predictors of mortality, while GTR was a predictor of improved survival (HR 0.04; 95% CI 0.005–0.3; $p = 0.002$). Interestingly, malignant transformation was not a predictor of mortality (HR 1.1; 95% CI 0.1–8.4; $p = 0.94$). On multivariate Cox regression survival analysis, GTR (HR 0.05; 95% CI 0.006–0.4;

p = 0.005) and leptomeningeal metastasis at presentation (HR 3.3, 95% CI 1.2–9.2; p = 0.025) remained statistically significant.

Next, we performed a Cox regression survival analysis to identify predictors of tumor recurrence or progression (Table 3). Median follow-up time was 2 years (IQR 0.8–4 years), during which 37.0% of the cohort experienced tumor recurrence or progression. By definition, malignant transformation was considered tumor progression and therefore not included in the statistical analysis due to collinearity. On univariate analysis, DIA pathology (HR 2.3; 95% CI 1.4–3.8; p = 0.002), leptomeningeal metastasis at presentation (HR 3.8; 95% CI 2.0–7.0; p < 0.001), and deep tumor location (HR 3.7; 95% CI 2.1–6.5; p < 0.001) were predictors of tumor recurrence / progression, while GTR was negatively associated with tumor recurrence / progression (HR 0.5; 95% CI 0.3–0.8; p = 0.003). Furthermore, chemotherapy administration was associated with tumor recurrence / progression (HR = 3.2; 95% CI 1.9–5.4; p < 0.001); however, this finding is likely association in nature, as patients may have been only considered candidates for chemotherapy following evidence of tumor recurrence / progression. On multivariate analysis, deep tumor location (HR 2.9; 95% CI 1.6–5.4; p = 0.001) and chemotherapy (HR 2.0; 95% CI 1.3–3.6; p = 0.017) remained statistically significant.

Discussion

DIA/DIGs most frequently occur in infants less than 24 months of age, affect males more often than females, and though rare, account for a significant proportion of intracranial neoplasms seen in the first year of life [10, 11]. In 1978, Friede reported a desmoplastic glial tumor of the medulla with extensive leptomeningeal metastases at presentation, which he proposed be called “gliofibroma” or “desmoplastic glioma” [12]. DIA was introduced as a separate entity by Taratuto, who described 6 infants with “superficial cerebral astrocytoma attached to dura” [13]. VandenBerg then reported on 11 infants with DIG in 1987, noting the mixed glial and neuronal histology [14]. These tumors have generally been associated with good prognosis, particularly when completely resected [15]. Because of the rarity of this tumor, its natural history, response to treatment, and prognostic factors are not well studied systematically in the literature. We therefore sought to address these issues by performing the first IPDMA for this disease.

DIA/DIGs commonly present in the periphery of the supratentorial compartment, consisting of a cystic component with a contrast-enhancing nodule, and can develop over time [16]. This entity more rarely presents as an intraventricular lesion, or as a mostly-solid sellar/hypothalamic region mass. In our survival analysis, we found that deep tumor location was a prognostic factor for increased mortality, and more importantly an independent predictor of shorter time to tumor recurrence.

Histologically, these tumors are marked by prominent desmoplasia within a dense stroma, as well as fibroblastic and neuroepithelial elements. Neoplastic cells are limited to the solid nodule and adjacent leptomeninges and parenchyma [15–19]. The presence of neuronal cells differentiates DIG from DIA. DIGs (but not DIAs) commonly involve rests of primitive ganglion cells that suggest anaplasia, so much so that the term “desmoplastic

neuroblastoma" was previously been used to describe the entity [20]. The presence of these primitive neuronal components do not appear to imply a more aggressive biology in DIA/DIG [6, 21–23]. Cases of craniospinal seeding or metastasis have been reported, [21–25] as have a few instances of malignant transformation, [26–28] but these had been thought to be infrequent events. Our data suggest that leptomeningeal metastasis at presentation predicted poorer survival.

DIA and DIG have not been previously differentiated in terms of natural history or expected outcomes. In this series, 46 cases were diagnosed specifically as DIA, with several describing a firm, rubbery, solid component without an associated peri-tumoral cyst. In our analysis, DIA pathology was more commonly found in deep locations and more commonly with leptomeningeal metastasis. Subsequently, they are also less susceptible to GTR. In survival analysis, we found that the DIA group had no differences in survival; however, they were associated with tumor recurrence/progression in our univariate analysis but was not an independent predictor in the multivariate analysis. Moreover, though the tumor biology is still most typically benign, patients have experienced poorer clinical outcomes after STR of DIA/DIG in comparison to GTR, and complete resection of these deep-seated tumors has thus far been unable to be achieved safely and consistently. This further contributes to the shortened time to tumor recurrence/progression for DIAs.

Because DIA/DIGs are classified by the WHO as grade I tumors, they have historically been considered potentially curative following GTR [29]. Indeed, tumor recurrences after GTR are rare. However, while the role of the extent of resection for the treatment of epilepsy associated with DIA/DIG has been well studied, its role from an oncologic perspective has not been well studied systematically. We have found in our survival analysis that GTR predicted survival on multivariate analysis and absence of tumor recurrence/progression on univariate analysis, suggesting a benefit of GTR from an oncologic perspective. The use of chemotherapy and radiation adjuvant therapy for DIA/DIG is uncommon, but was seen in 17.0 and 9.6% of this IPDMA cohort, respectively. Chemotherapy was statistically associated with tumor recurrence / progression, as it was likely reserved for those difficult cases in this cohort.

Although the sample size is limited, our data also found that tumors harboring *BRAF* mutations do not portend a worse prognosis in DIA/DIG. Further tissue sampling and genetic sequencing for these and other mutations may reveal important understanding about the biology of these tumors, and avenues for treatment in these difficult cases.

Although most DIA/DIGs are benign, 5.0% of this cohort progressed to aggressive tumors and developed anaplastic features. Most commonly in these scenarios, patients are found to have higher ki-67 indices and malignant transformation to GBM. We and others have previously found that malignant transformation was often associated with additional mutations such as TP53, ALK-EML4 fusion, and ATRX [7, 28]. It may be a feature that is under-reported, as it has been found in high percentage of patients who were followed long term [7]. In many cases of malignant transformation, the overall survival did not seem to be significantly impacted by the presence of anaplastic/malignant features, although this was frequently found at time of tumor recurrence.

Study limitations and future directions

This is a retrospective analysis of cases reported in the literature, and as such, have certain limitations. First, the diagnostic tools, imaging techniques, treatment modalities, and molecular studies across different historical eras have evolved, leading to inherent biases throughout the decades. Second, DIA/DIGs have historically been classified under different variants of glial-neuronal tumors; though every effort has been made to be as inclusive as possible in our search and screening strategy to identify all available cases of what would now be considered DIA/DIG to reduce selection bias. Third, each individual study reported a separate set of clinical information, and the amount and granularity of data in each field was variable, including the specific techniques of radiological or molecular assessments of each tumor. Finally, given the rarity of this condition, there are a significant number of studies consisting of single case reports, which may be published with a selection bias for interesting or unsual findings. At the same time, for the purposes of IPDMA, only the conglomerate clinical details presented in these small case reports or series allow for descriptive and survival analyses. To our knowledge, this is the first IPDMA of DIA/DIG tumors in the literature. Multi-institutional prospective studies that have larger cohorts of these patients are needed to better understand the clinical behavior of this disease and how it responds to various types of treatment.

Conclusion

Our IPDMA of the existing literature revealed that subtotal resection and leptomeningeal metastasis at presentation were significant predictors of mortality, and deep tumor location and chemotherapy were associated with tumor recurrence / progression in DIA/DIG. Our findings suggest that maximal safe resection should remain as the mainstay of treatment for these tumors. The need for chemotherapy and radiation in cases where complete resection is unable to be obtained does not appear to predict a higher mortality rate, but these adjuvant therapies should remain as options in cases of residual or recurrent tumor. Our findings also highlight the need for molecular testing of all DIA/DIG tumors, which might allow for the use of *BRAF* inhibitors or uncover alternative avenues to chemoradiation in refractory or recurrent cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The authors will provide data upon request.

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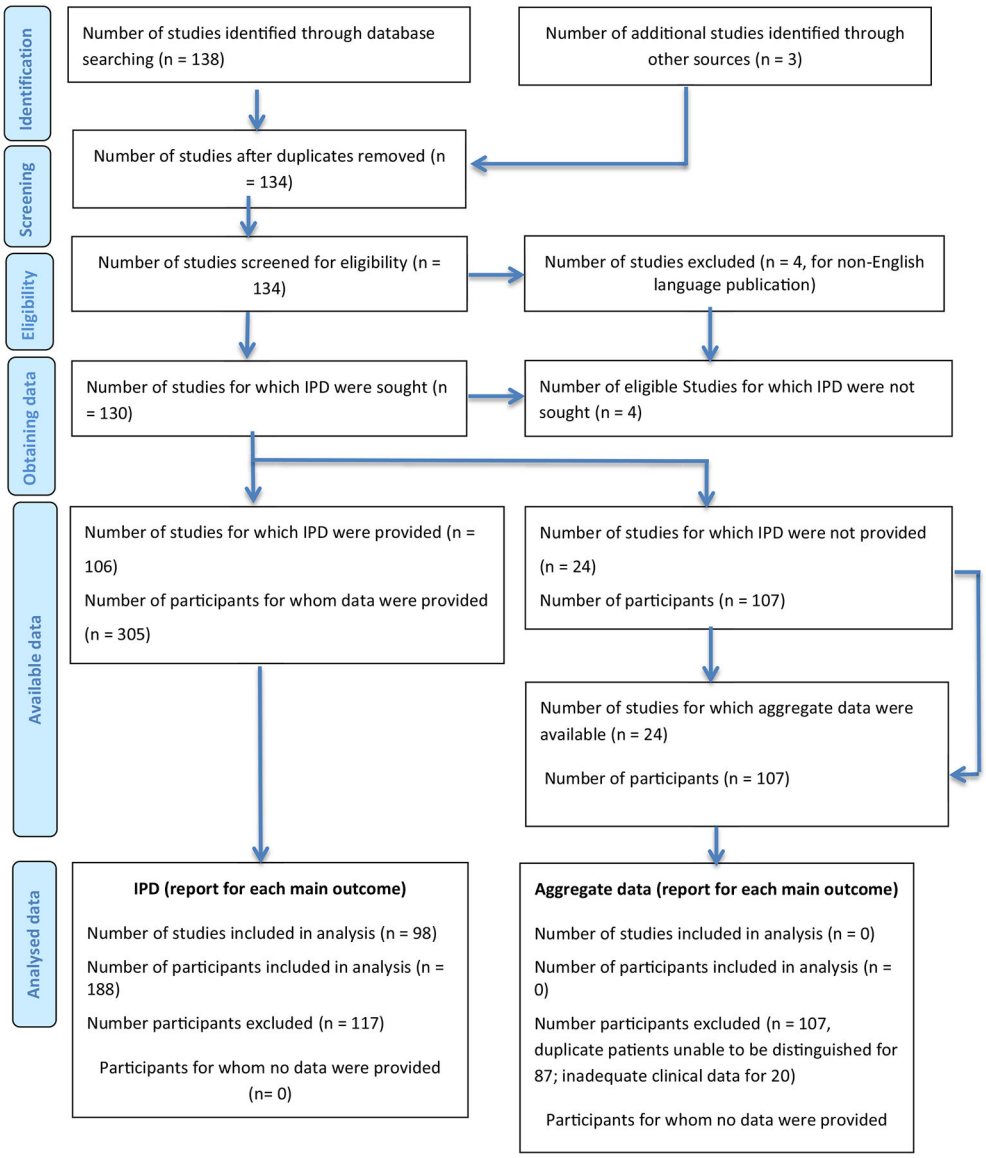

Fig. 1.
PRISMA flow chart of the studies included in this IPDMA

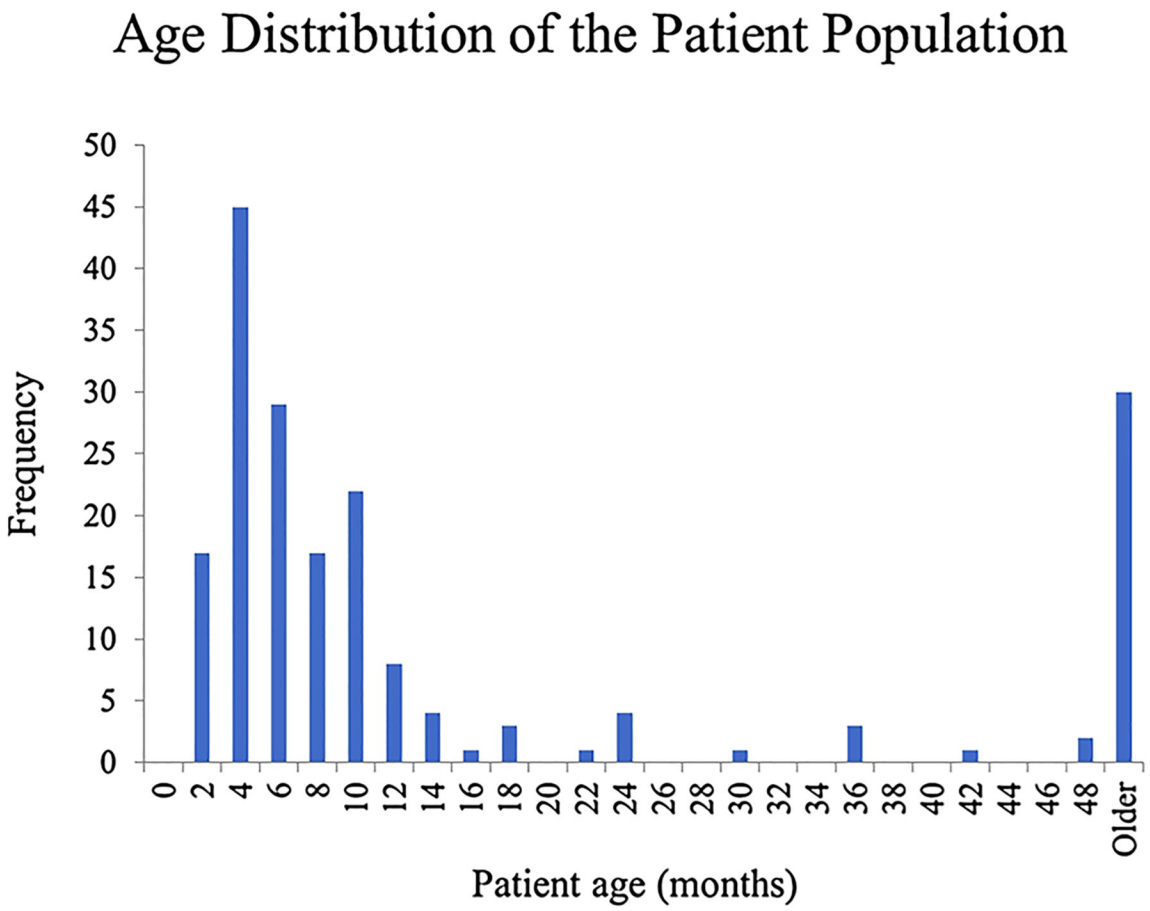

Fig. 2.
Age distribution of the population included in this IPDMA

Table 1

Characteristics of individuals included in the IPDMA (total n = 188)

Characteristic	Number	% Total
Gender (n = 185)		
Male	109	58.9
Female	76	41.1
Age, median months (IQR)	7 (4–14)	
Histopathology (n = 188)		
DIG/DNIG	128	68.1
DIA/DNIA/SCAAD/SCAI	46	24.5
DIT/DNT/DSNT	14	7.4
BRAF mutation (n = 55)		
BRAF V600D	4	7.3
Other BRAF mutation	2	3.6
No BRAF mutation	37	67.3
Leptomeningeal metastasis at presentation (n = 171)		
Yes	20	11.7
No	151	88.3
Tumor location (n = 163)		
Deep (tentorium, posterior fossa, intraventricular, thalamic, hypothalamic, and sella)	30	18.4
Superficial (lobar)	133	81.6
Extent of resection (n = 171)		
Gross total resection (GTR)	103	60.2
Subtotal resection (STR)	58	33.9
Biopsy	9	5.3
No surgery	1	0.6
Adjuvant therapy (n = 188)		
Any adjuvant therapy (radiation or chemotherapy)	43	22.9
Chemotherapy	32	17.0
Radiation therapy	18	9.6
Malignant transformation (n = 188)	9	5.0

DIA desmoplastic infantile astrocytoma, *DIG* desmoplastic infantile ganglioglioma, *DIT* desmoplastic infantile tumor, *DNIG* desmoplastic non-infantile ganglioglioma, *DNT* dysembryoplastic neuroepithelial tumor, *DSNT* desmoplastic supratentorial neuroepithelial tumors of infancy, *IQR* interquartile range, *SCAAD* superficial cerebral astrocytoma attached to dura, *SCAI* superficial cerebral astrocytoma of infancy

Table 2

Cox regression survival analysis for predictors of patient mortality

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Male gender	2.3	0.7–7.1	0.16			
Older age	1.0	0.9–1.0	0.42			
DIA pathology	1.2	0.4–3.8	0.74			
Gross total resection (GTR)	0.04	0.005–0.3	0.002 *	0.05	0.006–0.4	0.005 *
Leptomeningeal metastasis at presentation	7.8	2.8–21.9	< 0.001 *	3.3	1.2–9.2	0.025 *
Deep location of tumor	7.9	2.6–24.2	< 0.001 *			
Radiation therapy	1.2	0.3–5.4	0.78			
Chemotherapy	1.0	0.3–3.6	0.99			
Malignant transformation	1.1	0.1–8.4	0.94			

CI confidence interval, *DIA* desmoplastic infantile astrocytoma, *HR* hazard ratio

* Statistically significant

Table 3

Cox regression survival analysis for predictors of tumor recurrence or progression

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Male gender	0.9	0.6–1.5	0.74			
Older age	1.0	1.0–1.0	0.66			
DIA pathology	2.3	1.4–3.8	0.002*			
Gross total resection (GTR)	0.5	0.3–0.8	0.003*			
Leptomeningeal metastasis at presentation	3.8	2.0–7.0	< 0.001*			
Deep location of tumor	3.7	2.1–6.5	< 0.001*	2.9	1.6–5.4	0.001
BRAF mutation	1.1	0.4–3.2	0.86			
Radiation therapy	0.7	0.3–1.8	0.51			
Chemotherapy	3.2	1.9–5.4	< 0.001*	2.0	1.3–3.6	0.017

CI confidence interval, *DIA* desmoplastic infantile astrocytoma, *HR* hazard ratio

* Statistically significant