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ORIGINAL REPORT

Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries

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ABSTRACT

Purpose

Diffuse intrinsic pontine glioma (DIPG) is a brainstem malignancy with a median survival of < 1 year. The International and European Society for Pediatric Oncology DIPG Registries collaborated to compare clinical, radiologic, and histomolecular characteristics between short-term survivors (STSs) and long-term survivors (LTSs).

Materials and Methods

Data abstracted from registry databases included patients from North America, Australia, Germany, Austria, Switzerland, the Netherlands, Italy, France, the United Kingdom, and Croatia.

Results

Among 1,130 pediatric and young adults with radiographically confirmed DIPG, 122 (11%) were excluded. Of the 1,008 remaining patients, 101 (10%) were LTSs (survival ≥ 2 years). Median survival time was 11 months (interquartile range, 7.5 to 16 months), and 1-, 2-, 3-, 4-, and 5-year survival rates were 42.3% (95% CI, 38.1% to 44.1%), 9.6% (95% CI, 7.8% to 11.3%), 4.3% (95% CI, 3.2% to 5.8%), 3.2% (95% CI, 2.4% to 4.6%), and 2.2% (95% CI, 1.4% to 3.4%), respectively. LTSs, compared with STSs, more commonly presented at age < 3 or > 10 years (11% *v* 3% and 33% *v* 23%, respectively; $P < .001$) and with longer symptom duration ($P < .001$). STSs, compared with LTSs, more commonly presented with cranial nerve palsy (83% *v* 73%, respectively; $P = .008$), ring enhancement (38% *v* 23%, respectively; $P = .007$), necrosis (42% *v* 26%, respectively; $P = .009$), and extrapontine extension (92% *v* 86%, respectively; $P = .04$). LTSs more commonly received systemic therapy at diagnosis (88% *v* 75% for STSs; $P = .005$). Biopsies and autopsies were performed in 299 patients (30%) and 77 patients (10%), respectively; 181 tumors (48%) were molecularly characterized. LTSs were more likely to harbor a *HIST1H3B* mutation (odds ratio, 1.28; 95% CI, 1.1 to 1.5; $P = .002$).

Conclusion

We report clinical, radiologic, and molecular factors that correlate with survival in children and young adults with DIPG, which are important for risk stratification in future clinical trials.

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ASSOCIATED CONTENT

Appendix
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INTRODUCTION

Diffuse intrinsic pontine glioma (DIPG) is a malignant brainstem tumor of childhood for which median survival is < 1 year.[1] Long-term survival, historically defined as overall survival (OS) > 2 years, is reported in < 10% of patients.[1] Characteristics associated with longer survival include younger age, longer symptom latency, and absent ring enhancement on diagnostic magnetic resonance imaging.[1,2] Up to 90% of DIPGs harbor a pathognomonic point mutation in *H3F3A* (65% of tumors) or *HIST1H3B* (25% of tumors); the latter seems to confer longer survival. Ten percent of patients have a histone 3 wild-type tumor.[3]

Involved-field radiation therapy (RT) remains standard of care but confers only a 3- to 4-month survival advantage. Benefit from neoadjuvant[4] or adjuvant[2,5] chemotherapy has not been consistently confirmed in prospective trials.

The rarity and inconsistent classification of DIPG, an imaging-based diagnosis, have long hampered cross-cohort comparisons. The primary aim of this multinational collaboration between the International DIPG Registry (IDIPGR) and European Society for Pediatric Oncology DIPG Registry (SIOPE-DIPGR)[6,7] was to define clinical, radiologic, histologic, and molecular factors associated with short- and long-term survival in the largest cohort of centrally reviewed DIPGs to date.

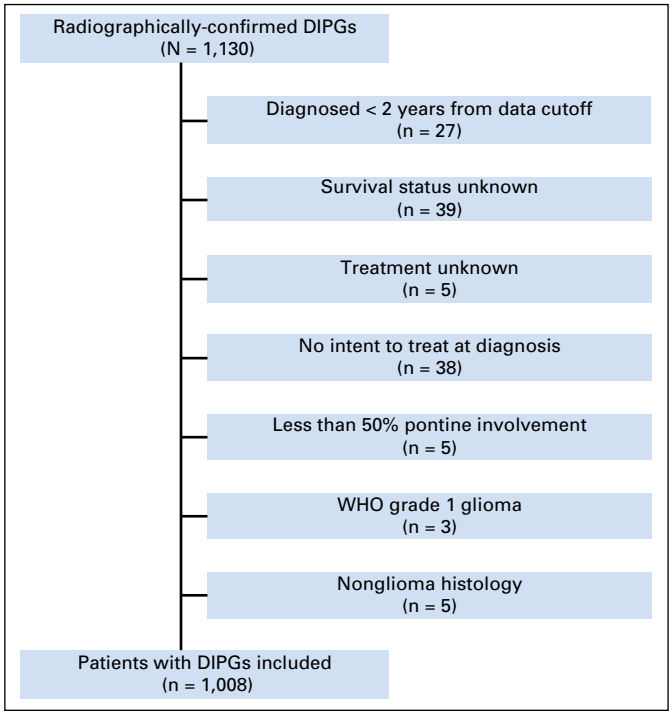


Fig 1. Flowchart of patients excluded from this study. DIPG, diffuse intrinsic pontine glioma.

MATERIALS AND METHODS

Study Population

The study was approved by the institutional review board at Cincinnati Children's Hospital Medical Center and included 1,130 patients with radiographically confirmed DIPG diagnosed from 1990 to 2015. IDIPGR patients (n = 409) were age 0 to 27 years from the United States, Canada, and Australia. SIOPE-DIPGR patients (n = 721) were age 0 to 21 years from the Netherlands, Germany, Austria, Switzerland, Italy, France, the United Kingdom, and Croatia. Patients were referred to the registries as previously described.[6,7] Exclusion criteria are listed in Figure 1. No patients with neurofibromatosis type 1 were included.

Clinical Variables

Clinical data were abstracted (J.B., B.C., S.E.M.V.v.Z., and N.C.) using standardized case report forms. Cerebellar signs included dysmetria, ataxia, dysarthria, or nystagmus. Pyramidal tract signs included mono-, hemi-, or quadriparesis; hyperreflexia; or positive Babinski sign. Because over survival (OS), defined as the time from diagnosis to death or last follow-up, is regarded as the most reliable outcome variable for DIPG, progression-free survival (PFS) was not reported. Short-term survivors (STSs), long-term survivors (LTSs), and very long–term survivors (VLTSs) had OS times of < 24, ≥ 24, and ≥ 60 months, respectively. Two LTSs (patients DIPG-0016 and DIPG-0081) lost to follow-up at our data cutoff (January 1, 2017) were included in primary statistical analyses.

Radiologic Variables

Anonymized diagnostic magnetic resonance imaging was centrally reviewed (M.W., B.B., E.S., R.C., J.L., and B.J.) and classified as typical or unlikely DIPG; the latter were excluded. Typical DIPGs arose from and diffusely involved ≥ 50% of the pons. Exclusionary features included focally exophytic morphology, marked diffusion restriction, or secondary brainstem involvement by a tumor centered elsewhere in the brain or spine. Diagnostic imaging from all LTSs and 10% of STSs was cross-validated by a neuroradiologist from the other registry. Metastatic disease, defined as noncontiguous tumor in the brain or spine, was reported by individual sites but not centrally reviewed.

Histopathologic and Molecular Variables

Histology was defined according to 2007 WHO criteria[8]; based on availability of tissue in the registries, 61 tumor specimens were centrally reviewed (C.F. and C.H.). Databases were queried for common genomic alterations in DIPG. Histone mutations were assessed by Sanger sequencing, whole-exome sequencing, or whole-genome sequencing, polymerase chain reaction, or immunohistochemistry to detect H3K27M-mutant protein or H3K27 trimethylation (H3K27me3). Mutations in *H3F3A* (H3.3 K27M) or *HIST1H3B* (H3.1 K27M) were considered mutually exclusive even if both were not evaluated.

Statistical Analyses

Patient characteristics were summarized using medians and ranges or frequencies and percentages. Univariable analyses were performed using the Fisher's exact test or Wilcoxon rank sum test. Multivariable logistic regression was performed on variables with < 15% missing data and univariable $P < .1$; however, transverse tumor dimension was excluded as a result of high correlation with craniocaudal dimension. For subgroup analyses, multivariable logistic regression models were used to determine subgroup significance and adjusted for confounding factors. Survival was estimated using the Kaplan-Meier method. Statistical evaluation was performed using R (Version 3.1.3). $P < .05$ was considered significant.

RESULTS

Survival

A total of 1,008 patients met inclusion criteria (IDIPGR, n = 374; SIOPE-DIPGR, n = 634). Median survival time was 11 months

(interquartile range, 7.5 to 16 months), and 1-, 2-, 3-, 4-, and 5-year OS rates were 42.3% (95% CI, 38.1% to 44.1%), 9.6% (95% CI, 7.8% to 11.3%), 4.3% (95% CI, 3.2% to 5.8%), 3.2% (95% CI, 2.4% to 4.6%), and 2.2% (95% CI, 1.4% to 3.4%), respectively. Characteristics of 101 LTSs (10%) and 16 VLTSs (1.6%) are shown in Figure 2 and Appendix Figure A1 (online only), respectively. Kaplan-Meier survival analyses for age, symptom duration, systemic therapy, histology, and molecular status are shown in Figure 3.

Clinical Presentation

Median age was 6.8 years (range, 0 to 26.8 years); 4% of patients were age < 3 years at diagnosis. Of patients with available data, 755 (82%) of 917, 468 (51%) of 915, and 567 (62%) of 920 patients presented with one or more cranial nerve (CN) palsy, pyramidal tract, or cerebellar sign, respectively. On univariable analysis (Table 1), LTSs were more likely to be age < 3 years (28% *v* 3% of STSs) or > 10 years (33% *v* 23% of STSs; $P < .001$) and had longer symptom duration at diagnosis. LTSs were less likely to present with CN palsy (72% *v* 83% of STSs; $P = .008$). Multivariable analyses (Table 2) confirmed association of age and symptom duration with long-term survival but failed to associate CN palsy with short-term survival.

Therapy

Thirty-eight patients (3%) who did not receive therapy at diagnosis (Appendix Fig A2A, online only) were excluded. Untreated patients were more often < 3 years old at diagnosis. Eleven patients underwent biopsy or autopsy. At progression, one patient received chemotherapy; no patients received RT. Median OS of untreated patients was 1 month (range, 0 to 135 months). Two patients were LTSs (both infants), including one who was alive 135 months after diagnosis (Appendix Fig A2B, online only).

The status of RT and systemic therapy was known for 968 patients; 721 patients (74%) received both RT and systemic therapy, 231 patients (24%) received RT alone, and 16 patients (2%) received systemic therapy alone. In univariable and multivariable analyses, LTSs more commonly received systemic therapy at diagnosis (88% *v* 75% for STSs; $P = .005$; odds ratio [OR], 3; 95% CI, 1.46 to 7.3; $P = .01$). Systemic therapy type was known for 702 patients (70%); 350 patients (50%) received cytotoxic therapy only, 193 patients (27%) received targeted therapy only, and 159 patients (23%) received both cytotoxic and targeted. On univariable analysis, type of targeted therapy yielded no survival difference (Table 1). However, multivariable logistic regression adjusted for age and symptom duration demonstrated greater odds of long-term survival with use of an epidermal growth factor receptor (EGFR) inhibitor (OR, 2.32; 95% CI, 1.1 to 4.82; $P = .03$) or bevacizumab (OR, 2.67; 95% CI, 1.09 to 6.55; $P = .03$), an anti–vascular endothelial growth factor (VEGF) antibody, at diagnosis (Table 2). Seventy-two patients (7%) underwent reirradiation at first or subsequent progression (as reported by individual sites). The rate of first progression recorded within 1 year of diagnosis was significantly lower in patients who underwent reirradiation compared with patients who did not (74% *v* 88%, respectively; $P = .007$).

Imaging

Table 1 lists diagnostic imaging characteristics. STSs demonstrated larger craniocaudal tumor dimension (43 *v* 40 mm for LTSs; $P = .04$) and higher rates of extrapontine extension (92% *v* 85% for LTSs; $P = .04$), tumor necrosis (45% *v* 26% for LTSs; $P = .009$), and ring enhancement (38% *v* 23% for LTSs; $P = .007$). Metastatic disease at diagnosis was reported in 18 STSs (2%) and no LTSs.

Histology and Molecular Characteristics

More SIOPE-DIPGR patients (39%) than IDIPGR patients (14%) underwent biopsy, and more IDIPGR patients (16%) than SIOPE-DIPGR patients (4%) underwent autopsy (Appendix Table A1, online only). LTSs from both registries were more often biopsied than STSs (38% *v* 28%, respectively; $P = .04$). Histology and WHO grade were known for 288 biopsy and 76 autopsy samples. WHO grade did not influence survival. Biopsy specimens included glioblastoma multiforme (GBM; n = 80), anaplastic astrocytoma (n = 76), anaplastic oligodendroglioma (n = 10), diffuse astrocytoma (n = 37), fibrillary astrocytoma (n = 4), oligodendroglioma (n = 2), low-grade astrocytoma (n = 8), and unknown (n = 71). Histology of autopsy tissue included GBM (n = 48), anaplastic astrocytoma (n = 12), diffuse astrocytoma (n = 3), and unknown (n = 13).

Of 376 patients from whom tissue was obtained, genomic data were available for 181 (48%) of patients (18% of the entire cohort; Data Supplement), including 21 LTSs (Fig 4). Global molecular assessment was undertaken for 44 patients (whole-genome sequencing, n = 16; whole-exome sequencing, n = 25; 450k methylation array, n = 3), whereas 98 patients underwent limited genomic sequencing (Sanger, n = 80; other targeted platform, n = 18), and 36 patients underwent immunohistochemistry alone. H3.1 K27M was associated with longer median OS (15 months) and long-term survival in multivariable analysis (OR, 1.28; 95% CI, 1.1 to 1.5; $P = .002$). In contrast, H3.3 K27M was associated with short-term survival (OR, 0.88; 95% CI, 0.78 to 0.99; $P = .04$; median survival, 10.4 months). Patients with H3 wild-type tumors (n = 26) had a median OS of 10.5 months. WHO grade did not correlate with histone mutation status. *TP53* and *ACVR1* mutations were not associated with survival. Of the 50 patients age > 10 years at diagnosis, who as a group demonstrated higher likelihood of long-term survival, 38 (78%) harbored H3.3 K27M, nine (18%) were H3 wild-type, and only three (6%) had H3.1 K27M.

DISCUSSION

This study confirms the relevance of some previously reported survival-associated factors in patients with DIPG and offers unique insight into 101 LTSs (including 16 VLTSs). Median survival for all 1,008 patients was 11 months.[1,5] Median survival times of LTSs and VLTSs were 33 months (range, 24 to 156 months) and 78 months (range, 60 to 156 months), respectively. Of 16 surviving patients, two were lost to follow-up but were LTSs at the time of last contact (patients DIPG-0016 and DIPG-0081; OS, 33 and 36 months). The 2-year OS rate of 9.6% in this study was consistent with large retrospective studies[2,5] that reported 9.2% and 9% 2-year OS rates in 153 and 316 patients with DIPG, respectively. The 1-year OS rate in our study (42.3%) is comparable to that reported by Hassan et al[9] in a meta-analysis of 2,336 pediatric patients with high-grade brainstem glioma (41%); however, the 2- and 3-year OS rates of 15.3% (95% CI, 12% to 20%) and 7.3% (95% CI, 5.2% to 10%) in

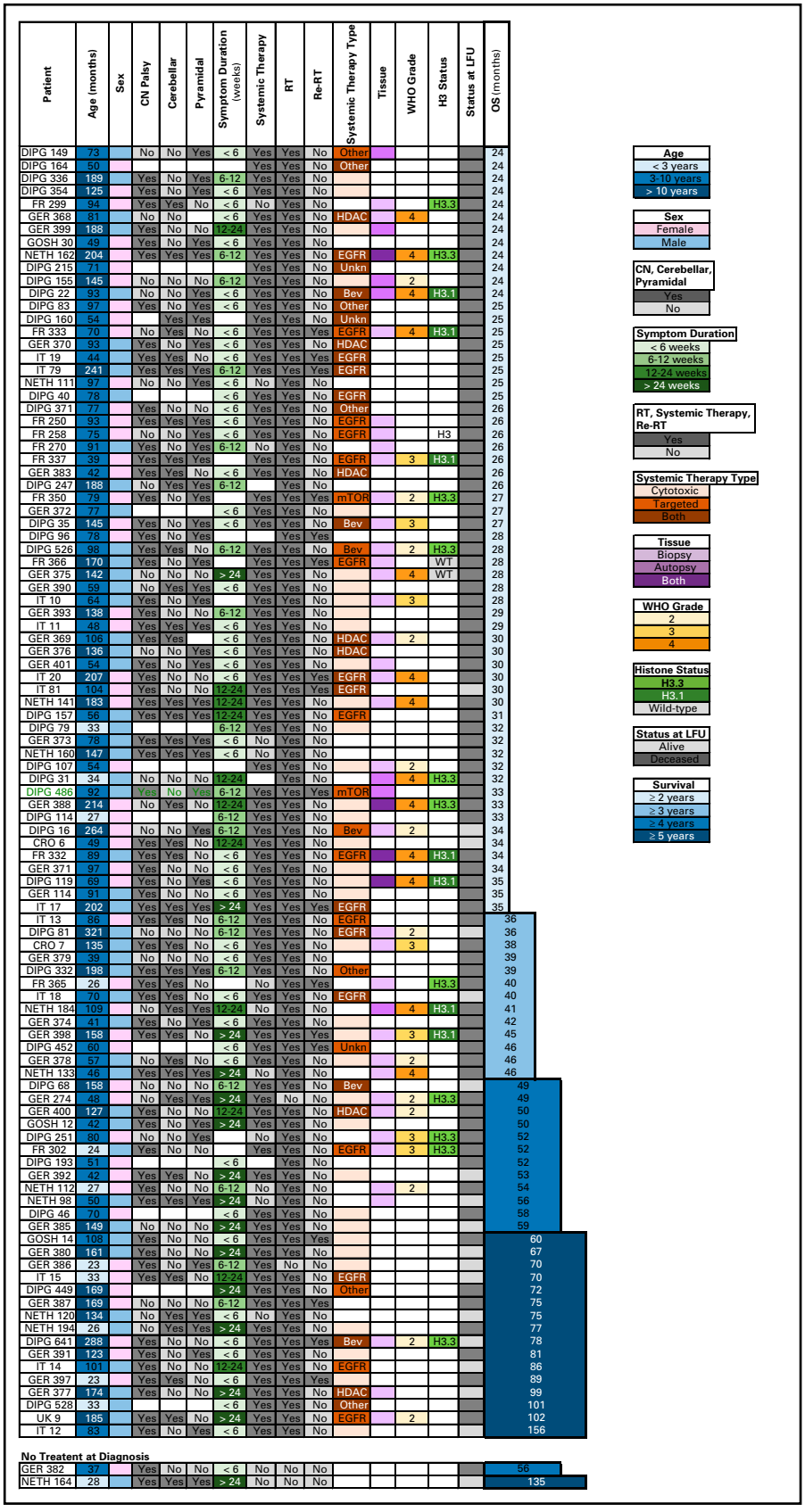
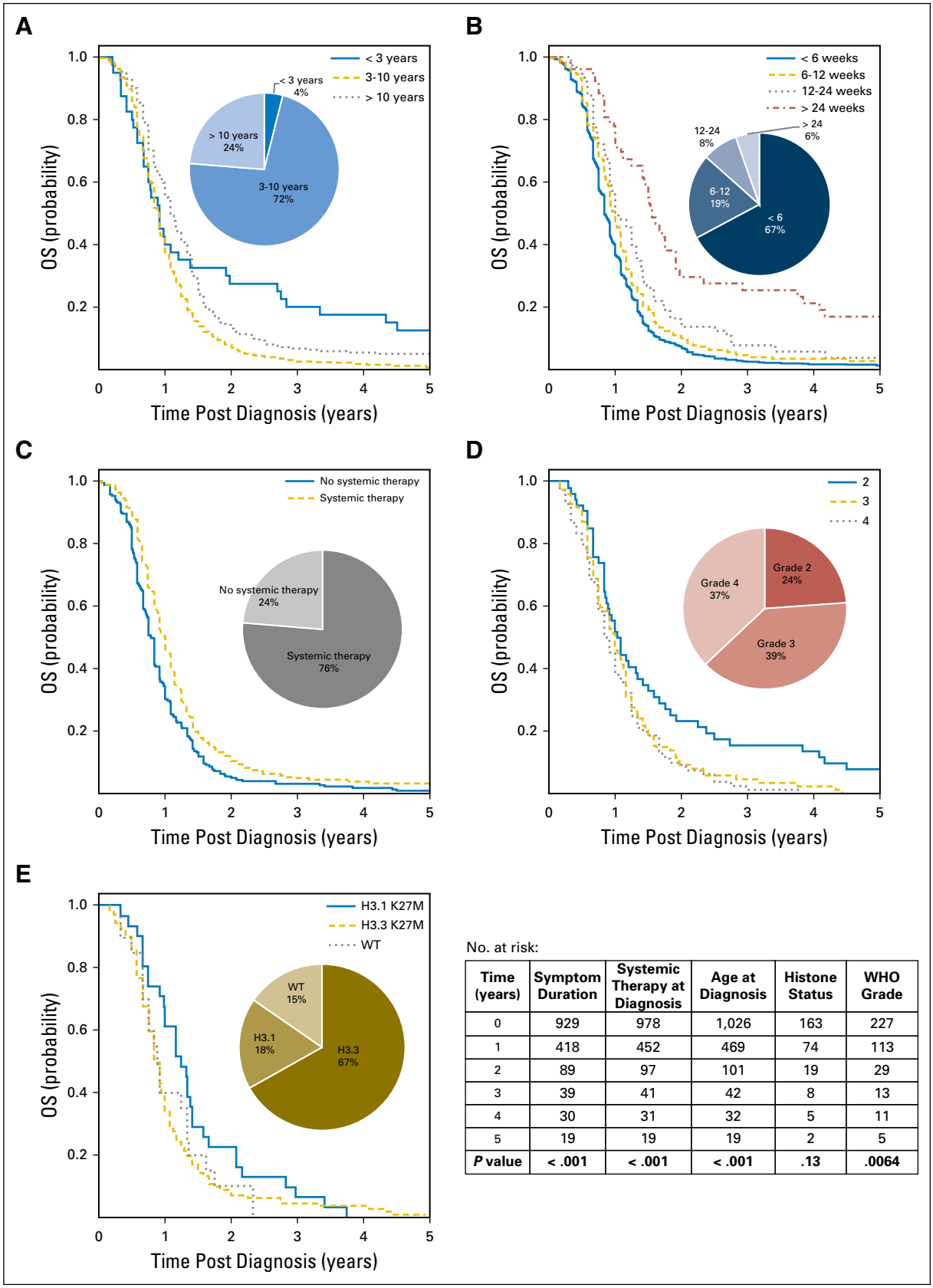


Fig 2. Clinical, histologic, and molecular characteristics of long-term survivors of diffuse intrinsic pontine glioma. Bev, bevacizumab; CN, cranial nerve; CRO, Croatia; DIPG, International DIPG Registry; EGFR, epidermal growth factor receptor; FR, France; GER, Germany, Switzerland, Austria; GOSH, Great Ormond Street Hospital; HDAC, histone deacetylase inhibitor; IT, Italy; LFU, last follow-up; mTOR, mammalian target of rapamycin inhibitor; NETH, the Netherlands; OS, overall survival; Re-RT, reirradiation; RT, radiation therapy; UK, United Kingdom; Unkn, unknown.



No. at risk:

Time (years)	Symptom Duration	Systemic Therapy at Diagnosis	Age at Diagnosis	Histone Status	WHO Grade
0	929	978	1,026	163	227
1	418	452	469	74	113
2	89	97	101	19	29
3	39	41	42	8	13
4	30	31	32	5	11
5	19	19	19	2	5
***P* value**	**< .001**	**< .001**	**< .001**	**.13**	**.0064**

Fig 3. Kaplan-Meier curves representing overall survival (OS) based on (A) patient age (years), (B) symptom duration (weeks), (C) systemic therapy at diagnosis, (D) WHO grade, or (E) histone status. WT, wild type.

Table 1. Results of Univariable Analyses Comparing Clinical, Radiologic, and Histologic Characteristics of Long- and Short-Term Survivors of Diffuse Intrinsic Pontine Glioma

Characteristic	LTSs (n = 101)	STSs (n = 907)	*P*
Clinical			
Registry, No. (%)			.39
International	33 (9)	341 (91)	
SIOPE	68 (11)	566 (89)	
Sex, No. (%)			.46
Male	51 (50)	420 (46)	
Female	50 (50)	485 (54)	
Race, No. (%)			.43
African	4 (9)	43 (12)	
Asian	2 (4)	14 (4)	
White	36 (80)	237 (69)	
Other	3 (7)	50 (15)	
Median age, years (range)	7.2 (1.9-26.8)	6.8 (0-26.5)	.61
Age, years, No. (%)			< .001
< 3	11 (11)	29 (3)	
3-10	57 (56)	668 (74)	
> 10	33 (33)	205(23)	
Symptom duration, weeks, No. (%)			< .001
< 6	45 (51)	564 (69)	
6-12	19 (21)	156 (19)	
12-24	11 (12)	62 (8)	
> 24	14 (16)	35 (4)	
Symptoms at diagnosis, No. (%)			
Cranial nerve palsy			.008
Yes	63 (73)	692 (83)	
No	25 (27)	137 (17)	
Pyramidal tract sign			.5
Yes	39 (44)	429 (52)	
No	50 (56)	397 (48)	
Cerebellar sign			.08
Yes	46 (53)	521 (63)	
No	41 (47)	312 (37)	
CSF diversion, No. (%)			1.00
Yes	22 (22)	196 (22)	
No	79 (78)	709 (78)	
Systemic therapy at diagnosis, No. (%)			.005
Yes	85 (88)	644 (75)	
No	12 (12)	214 (25)	
Category of systemic therapy, No. (%)			.07
Cytotoxic chemotherapy	36 (44)	314 (51)	
Targeted chemotherapy	19 (23)	174 (28)	
Both	27 (33)	132 (21)	
Chemotherapy type, No. (%)			
Cytotoxic	63 (56)	446 (60)	.43
EGFR inhibitor	21 (19)	114 (15)	.14
HDAC inhibitor	8 (7)	54 (7)	.68
mTOR inhibitor	2 (2)	14 (2)	1.00
Bevacizumab	8 (7)	44 (6)	.37
Other targeted agent	10 (9)	88 (12)	.74
Radiologic			
Median tumor size, mm (range)			
AP	36 (18-57)	36 (14-70)	.98
Transverse	43 (15-76)	45 (17-81)	.08
CC	40 (20-88)	43 (16-107)	.04
Median pons size, mm (range)			
AP	36 (21-50)	35 (20-58)	.12
Transverse	49 (31-62)	48 (22-78)	.62
Extrapontine extension, No. (%)			.04
Yes	78 (86)	739 (92)	
No	13 (14)	60 (8)	
Hemorrhage, No. (%)			.35
Yes	11 (14)	136 (19)	
No	68 (86)	588 (81)	
Necrosis, No. (%)			.009
Yes	20 (26)	306 (42)	
No	56 (74)	424 (58)	
Hydrocephalus, No. (%)			1.00
Yes	14 (18)	136 (18)	
No	65 (82)	632 (82)	
Tumor margin, No. (%)			.14
Ill defined	64 (75)	605 (82)	
Well defined	21 (25)	132 (18)	
Ring enhancement, No. (%)			.007
Yes	19 (23)	281 (38)	
No	63 (77)	457 (62)	
Histologic			
Biopsy, No. (%)			.03
Yes	38 (38)	249 (28)	
No	61 (62)	652 (72)	
Autopsy, No. (%)			.04
Yes	11 (18)	65 (10)	
No	49 (82)	597 (90)	
WHO grade, No. (%)			.08
2	12 (41)	40 (21)	
3	9 (31)	76 (40)	
4	8 (28)	73 (39)	

(continued in next column)

Table 1. Results of Univariable Analyses Comparing Clinical, Radiologic, and Histologic Characteristics of Long- and Short-Term Survivors of Diffuse Intrinsic Pontine Glioma (continued)

Abbreviations: AP, anterior-posterior; CC, craniocaudal; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; LTSs, long-term survivors; mTOR, mammalian target of rapamycin; SIOPE, European Society for Pediatric Oncology; STSs, short-term survivors.

their study were higher than those in our study (9.6% and 4.3%, respectively), likely reflecting the heterogeneity of their cohort, some whom may not have true DIPGs.

Previously, 43 VLTSs had been reported in the literature.[1,10-15] In Appendix Figure A1, we compare the characteristics of 22 previously published VLTSs to our 16 VLTSs, including eight (0.02% of the total cohort) who are alive with a median follow-up time of 6.5 years (range, 5 to 13 years). Our 5-year OS rate of 2.3% is comparable to the rate of 2.6% reported by Jackson et al[1] in 191 patients with DIPG; however, two of their five VLTSs would have been excluded from our study for atypical magnetic resonance imaging features. Freeman et al[12] reported nine VLTSs (6.9%) among 130 patients with DIPG treated with hyperfractionated RT (Pediatric Oncology Group 8495 trial), although only four of these patients (3%) would have met inclusion criteria in our study.

Age < 3 or > 10 years, longer symptom latency, lack of CN palsy, and systemic therapy at diagnosis were predictors of long-term survival. Of 41 patients age < 3 years at diagnosis, 36 received first-line RT with or without systemic therapy and five received systemic therapy alone. Although median OS for children age < 3 years (11 months) was the same as the entire cohort, a greater proportion was LTSs or VLTSs. Other studies have reported similar findings.[1,2,5,16] Broniscer et al[17] described 10 DIPG patients age < 3 years who received RT with or without chemotherapy (n = 8) or chemotherapy only (n = 2) at diagnosis (n = 6) or progression (n = 4). Five patients (50%) were LTSs, including one treated without RT. Wagner et al[5] similarly reported higher median survival in 13

Table 2. Results of Multivariable Cox Proportional Analysis of Clinical, Radiologic, and Molecular Variables Predicting Survival

Variable	Odds Ratio (95% CI)	*P*
Clinical		
Age, years		.02
< 3	2.82 (1.06 to 10.28)	
3-10	1.0	
> 10	2.24 (1.27 to 3.96)	
Symptom duration, weeks		< .001
< 6	1.0	
6-12	1.49 (0.76 to 2.92)	
12-24	2.43 (1.04 to 5.75)	
> 24	5.7 (2.77 to 14.54)	
Cranial nerve palsy		.08
Yes	0.57	
No	1.0	
Systemic therapy at diagnosis		.01
Yes	3 (1.46 to 7.3)	
No	1.0	
Category of systemic therapy		.14
Cytotoxic chemotherapy	1.0	
Targeted chemotherapy	1.03 (0.51 to 2.09)	
Both	1.84 (0.99 to 3.41)	
Systemic therapy type		
Cytotoxic	1.59 (0.73 to 3.45)	.24
EGFR inhibitor	2.32 (1.1 to 4.82)	.03
HDAC inhibitor	1.49 (0.62 to 3.6)	.38
mTOR inhibitor	0.98 (0.11 to 8.66)	.98
Bevacizumab	2.67 (1.09 to 6.55)	.03
Other targeted agent	0.71 (0.22 to 2.28)	.56
Radiologic		
Tumor dimension, mm		.58
AP	—	
Transverse	0.99 (0.96 to 1.02)	
CC	—	
Extrapontine extension		.91
Yes	0.95 (0.36 to 2.43)	
No	1.0	
Molecular		
H3F3A mutation		.04
Yes	1.0	
No	1.14 (1.01 to 1.28)	
HIST1H3B mutation		.002
Yes	1.0	
No	0.78 (0.67 to 0.91)	
ACVR1 mutation		.09
Yes	1	
No	0.75 (0.54 to 1.03)	
TP53 mutation		.36
Yes	1	
No	0.92 (0.76 to 1.1)	

NOTE. Necrosis, enhancement, and WHO grade were excluded because > 15% of data for these variables were missing. Types of systemic therapy are not mutually exclusive and were not excluded for multiple therapies.

Abbreviations: AP, anterior-posterior; CC, craniocaudal; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin.

children with DIPG age < 4 years compared with older children (13.6 *v* 10 months); only eight patients (61%) received RT. Although limitations to our data precluded making conclusions about biologic differences in this young age group, we postulate that unique mechanisms, such as potently oncogenic *NTRK* fusions described in infantile midline high-grade gliomas,[18] may underlie this observed survival advantage.

Patients age > 10 years at diagnosis had longer median OS (13 months) and were more likely to be LTSs. Bailey et al[19] similarly reported five LTSs (all > 9 years old) among 43 patients with radiographically confirmed DIPG. In contrast, Veldhuijzen van Zanten et al[16] reported no difference in OS between patients age 9 to 18 years versus younger patients. Although pathogenic mechanisms, such as low-grade histology or *IDH* mutation may influence survival in older patients, 78% of patients > 10 years old in our study harbored the poor prognostic H3.3 K27M mutation. Clinical and molecular characteristics for patients age > 18 years (n = 13) were also similar to their younger counterparts (Appendix Fig A3, online only).

Consistent with prior reports,[1,2] the presence of symptoms for > 24 weeks at diagnosis was strongly associated with longer survival in univariable and multivariable analyses. CN palsy at diagnosis predicted shorter survival in univariable but not multivariable analysis. Previous studies reporting association of CN palsy with shorter survival included all brainstem tumors, not just DIPG, and/or diagnosis based on computed tomography scan, making comparison difficult.[20]

Neoadjuvant or adjuvant systemic therapy correlated with long-term survival in both univariable and multivariable analyses. This finding differs from the long-standing view that systemic therapy provides no survival benefit for DIPG, a principle largely based on small, nonrandomized clinical trials. Effective cross-comparison of therapeutic studies for DIPG has been hindered by wide variation in inclusion criteria, as demonstrated in studies by Hargrave et al[21] and Jansen et al[22] in which only six of 29 DIPG-specific therapeutic trials between 1984 and 2012 had comparable eligibility. In a randomized trial, Wagner et al[5] reported better median OS in patients with DIPG treated with adjuvant chemotherapy after RT (11.3 months) compared with patients treated with RT alone (9.5 months; $P = .03$). Similarly, others have reported superior median OS with use of adjuvant or neoadjuvant chemotherapy.[4]

Multivariable logistic regression demonstrated higher odds of long-term survival with use of EGFR inhibitors (eg, gefitinib, erlotinib, nimotuzumab, rindopepimut, cetuximab) or bevacizumab at diagnosis. A phase II study of gefitinib with RT in newly diagnosed patients with DIPG noted 2-year OS of 19.6% with PFS > 36 months in three patients.[23] In a biopsy-mandated phase I study of erlotinib with RT, EGFR overexpression trended toward longer PFS (10.1 months *v* 6.3 months in patients without EGFR overexpression; $P = .058$) but not OS.[24] Despite only modest activity of nimotuzumab in progressive DIPG, two patients lived for 663 and 481 days from the start of therapy.[25]

Despite efficacy in adult GBM, bevacizumab has shown little activity in pediatric trials for newly diagnosed[26] or progressive DIPG[27] (median PFS, 2.3 months). However, in a phase I trial of vandetanib, a selective vascular endothelial growth factor receptor receptor 2 (VEGFR2) and EGFR inhibitor, in newly diagnosed DIPG, Broniscer et al[28] reported 2-year OS of 21.4%, and higher levels of plasma VEGF were associated with longer PFS ($P = .02$). Although numbers were too small to assess patient outcomes based on genomically matched targeted therapy, our findings support prospective assessment of biopsy tissue to define potential therapeutic targets, as recently undertaken in two multi-institution, multinational trials (ClinicalTrials.gov identifiers: NCT01182350 and NCT02233049).

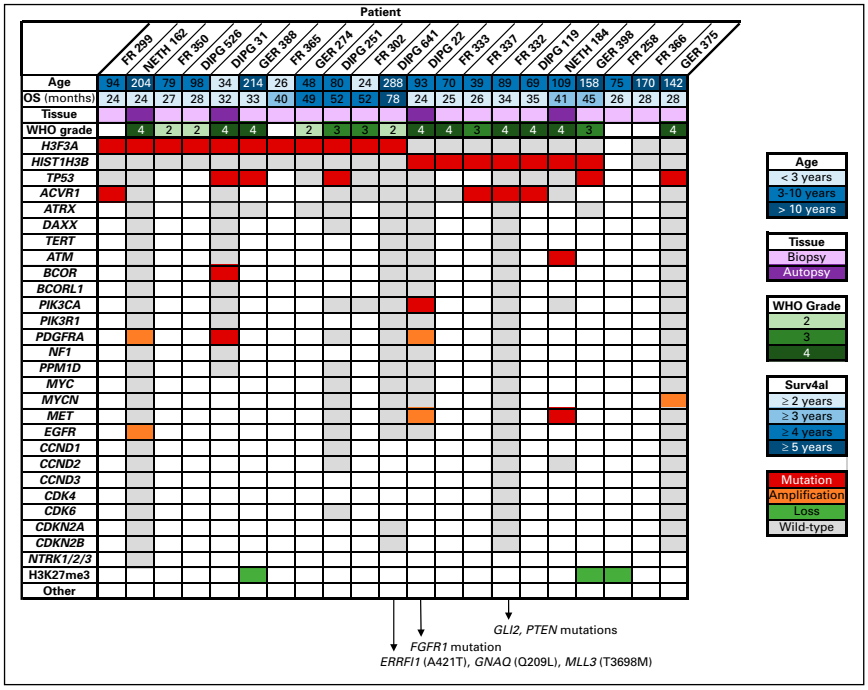


Fig 4. Genomic aberrations in long-term survivors of diffuse intrinsic pontine glioma (DIPG). DIPG, International DIPG Registry; FR, France; GER, Germany, Switzerland, Austria; NETH, the Netherlands; OS, overall survival.

Janssens et al[29] reported improved OS in 31 children with DIPG who received reirradiation at first progression (13.7 months) compared with a matched control cohort (10.3 months) despite similar PFS (8.2 *v* 7.7 months, respectively). Progression was not defined or centrally reviewed in our study; however, we noted that the proportion of patients with recorded progression within 1 year of diagnosis was significantly lower among patients who underwent reirradiation compared with those who did not, suggesting potential clinician bias to recommend reirradiation to patients with a more indolent disease course or potentially greater sensitivity to initial RT in patients who ultimately received reirradiation. As postulated by others,[30] increased RT sensitivity may be a manifestation of distinct biology. We did not report reirradiation-based outcomes given limitations conferred by analysis of registry data; more robust analysis of the effect of reirradiation in patients with DIPG would be best assessed prospectively in the context of a clinical trial.

On the basis of the radiographic definition of DIPG by Barkovich et al,[31] patients with < 50% pontine involvement (n = 5) were excluded. Similar to a prior report,[5] these patients had better median OS (20 months), and two patients were LTSs. Greater craniocaudal tumor dimension and extrapontine extension were associated with shorter survival; the former finding contrasts with a report by Poussaint et al,[32] in which larger tumor at diagnosis was associated with longer survival.

As previously described,[32] tumor necrosis and ring enhancement were associated with short-term survival in univariable analysis. Multivariable analysis was not performed because > 15% of data were missing for each variable, precluding comparison of our findings to the validated multiparametric prediction model published by Jansen et al.[2]

DIPG biology has been intensely studied since discovery of first-in-human histone mutations in 2012.[15] Our findings confirm the independent association of H3.1 K27M and H3.3 K27M with long- and short-term survival, respectively.[3,15] Median OS did not significantly differ between histone wild-type and mutant DIPGs; this contrasts with the report by Khuong-Quang et al[15] of longer median OS (4.59 years) for patients with histone wild-type tumors.

In univariable analysis, WHO grade did not differ between LTSs and STSs (Table 1), but on Kaplan-Meier analysis, WHO grade 2 was associated with longer survival (Fig 3D). In the most recent WHO classification of CNS tumors,[33] K27M-mutant midline gliomas are classified as WHO grade 4 regardless of histology, making this point less relevant. Tumors classified as primitive neuroectodermal tumors (now called embryonal tumor not otherwise specified) may represent true embryonal mimics of DIPG or result from sampling error in the context of intratumoral heterogeneity. Embryonal pontine tumors often demonstrate sharp margination and eccentric location, whereas others have radiologic characteristics indistinguishable from DIPG,[34] like those excluded from our study (Appendix Table A2, online only).

A limitation of this study is use of disease-specific registry data, which are susceptible to enrollment bias on the part of participating institutions (which tend to be large academic centers) and patients or families who self-refer. Variation in standards of care between countries and institutions may have also influenced findings. Anonymity of registry data makes some overlap of registry patients with those previously reported possible, biasing our findings toward similarity with published literature because they are not completely independent cohorts. The primary strength of this study is mandated central review of diagnostic imaging with cross-validation by highly experienced pediatric neuroradiologists and use of standardized case report forms. To our knowledge, this study represents the largest, most comprehensively annotated cohort of radiographically confirmed DIPGs reported, offering the most accurate rates of long- and very long–term survival for this rare tumor. Identification of robust survival-associated factors in this study is vital for development of prognostic subgroups and emphasizes patient subsets from whom the most could be learned from analyzing pretreatment biopsy

tissue. Understanding biologic differences that confer survival advantage in DIPG paves the road toward development of subgroup-specific therapies that, when implemented in the context of clinical trials, may improve outcomes for this devastating disease.

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Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries

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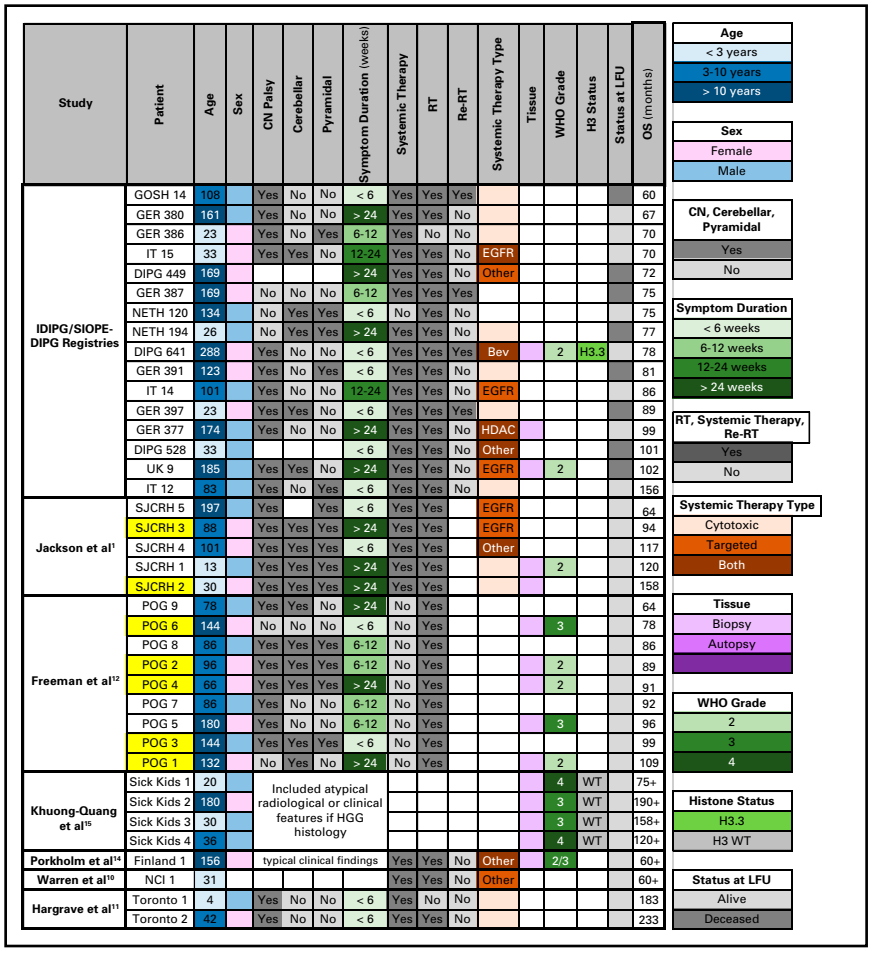
Appendix



Study	Patient	Age	Sex	CN Palsy	Cerebellar	Pyramidal	Symptom Duration (weeks)	Systemic Therapy	RT	Re-RT	Systemic Therapy Type	Tissue	WHO Grade	H3 Status	Status at LFU	OS (months)
IDIPG/SIOPE-DIPG Registries	GOSH 14	108		Yes	No	No	< 6	Yes	Yes	Yes						60
	GER 380	161		Yes	No	No	> 24	Yes	Yes	No						67
	GER 386	23		Yes	No	Yes	6-12	Yes	No	No						70
	IT 15	33		Yes	Yes	No	12-24	Yes	Yes	No	EGFR					70
	DIPG 449	169					> 24	Yes	Yes	No	Other					72
	GER 387	169		No	No	No	6-12	Yes	Yes	Yes						75
	NETH 120	134		No	Yes	Yes	< 6	No	Yes	No						75
	NETH 194	26		No	Yes	Yes	> 24	Yes	Yes	No						77
	DIPG 641	288		Yes	No	No	< 6	Yes	Yes	Yes	Bev		2	H3.3		78
	GER 391	123		Yes	No	Yes	< 6	Yes	Yes	No						81
	IT 14	101		Yes	No	No	12-24	Yes	Yes	No	EGFR					86
	GER 397	23		Yes	Yes	No	< 6	Yes	Yes	Yes						89
	GER 377	174		Yes	No	No	> 24	Yes	Yes	No	HDAC					99
	DIPG 528	33					< 6	Yes	Yes	No	Other					101
	UK 9	185		Yes	Yes	No	> 24	Yes	Yes	No	EGFR		2			102
	IT 12	83		Yes	No	Yes	< 6	Yes	Yes	No						156
Jackson et al[1]	SJCRH 5	197		Yes		Yes	< 6	Yes	Yes		EGFR					64
	SJCRH 3	88		Yes	Yes	Yes	> 24	Yes	Yes		EGFR					94
	SJCRH 4	101		Yes	Yes	Yes	< 6	Yes	Yes		Other					117
	SJCRH 1	13		Yes	Yes	Yes	> 24	Yes	Yes				2			120
	SJCRH 2	30		Yes	Yes	Yes	> 24	Yes	Yes							158
Freeman et al[12]	POG 9	78		Yes	Yes	No	> 24	No	Yes							64
	POG 6	144		No	No	No	< 6	No	Yes				3			78
	POG 8	86		Yes	Yes	Yes	6-12	No	Yes							86
	POG 2	96		Yes	Yes	Yes	6-12	No	Yes				2			89
	POG 4	66		Yes	Yes	Yes	> 24	No	Yes				2			91
	POG 7	86		Yes	No	No	6-12	No	Yes							92
	POG 5	180		Yes	No	No	6-12	No	Yes				3			96
	POG 3	144		Yes	Yes	Yes	< 6	No	Yes							99
	POG 1	132		No	Yes	No	> 24	No	Yes				2			109
Khuong-Quang et al[15]	Sick Kids 1	20		Included atypical radiological or clinical features if HGG histology									4	WT		75+
	Sick Kids 2	180											3	WT		190+
	Sick Kids 3	30											3	WT		158+
	Sick Kids 4	36											4	WT		120+
Porkholm et al[14]	Finland 1	156		typical clinical findings				Yes	Yes	No	Other		2/3			60+
Warren et al[10]	NCI 1	31						Yes	Yes	No	Other					60+
Hargrave et al[11]	Toronto 1	4		Yes	No	No	< 6	Yes	No	No						183
	Toronto 2	42		Yes	No	No	< 6	Yes	Yes	No						233

Fig A1. Very long–term survivors of diffuse intrinsic pontine glioma in the current study compared with those described in the literature. Yellow highlight indicates atypical radiologic features that would have been excluded in the current study. Bev, bevacizumab; CN, cranial nerve; DIPG, diffuse intrinsic pontine glioma; EGFR, epidermal growth factor; GER, Germany, Switzerland, Austria; GOSH, Great Ormond Street Hospital; HDAC, histone deacetylase inhibitor; HGG, high-grade glioma; IDIPGR, International Diffuse Intrinsic Pontine Glioma Registry; IT, Italy; LFU, last follow-up; NCI, National Cancer Institute; NETH, the Netherlands; OS, overall survival; POG, Pediatric Oncology Group; Re-RT, reirradiation; RT, radiation therapy; SIOPE, European Society for Pediatric Oncology; SJCRH, St Jude Children's Research Hospital; UK, United Kingdom; WT, wild type.

A

Clinical Variables	**Untreated** (n = 38)	**Treated** (n = 1,008)
LTS, No. (%)		
Yes	2 (5)	101 (10)
No	36 (95)	907 (90)
Age, years		
Median	6.3 (0-15.4)	6.8 (0-26.8)
< 3	10 (26%)	40 (4%)
≥ 3	28 (74%)	963 (96%)
Symptom duration, weeks		
< 6	26 (68%)	609 (67%)
6-12	8 (21%)	175 (19%)
12-24	1 (4%)	73 (8%)
> 24	3 (8%)	49 (6%)
Symptoms at diagnosis, No. (%)		
Cranial nerve palsy		
Yes	26 (79)	755 (82)
No	7 (21)	162 (18)
Pyramidal tract sign		
Yes	17 (52)	429 (52)
No	16 (48)	397 (48)
Cerebellar sign		
Yes	20 (62)	521 (63)
No	12 (38)	312 (37)
Median OS, months (range)	1 (0-135)	11 (0-167)

B

Patient	GER 382	NETH 164
Age (months)	37	28
Sex	Female	Male
CN palsy	Yes	Yes
Cerebellar	No	Yes
Pyramidal	No	Yes
Symptom duration (weeks)	< 6	> 24
Chemotherapy	No	No
RT	No	No
Re-RT	No	No
Status at LFU	Deceased	Alive
OS (months)	56	135

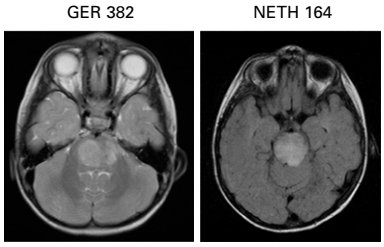


Fig A2. (A) Comparison of characteristics of patients who received therapy or did not receive therapy at diagnosis. (B) Magnetic resonance images and clinical characteristics of two long-term survivors (LTSs) of diffuse intrinsic pontine glioma who did not receive therapy. CN, cranial nerve; GER, Germany, Switzerland, Austria; LFU, last follow-up; NETH, the Netherlands; OS, overall survival; Re-RT, reirradiation; RT, radiation therapy.

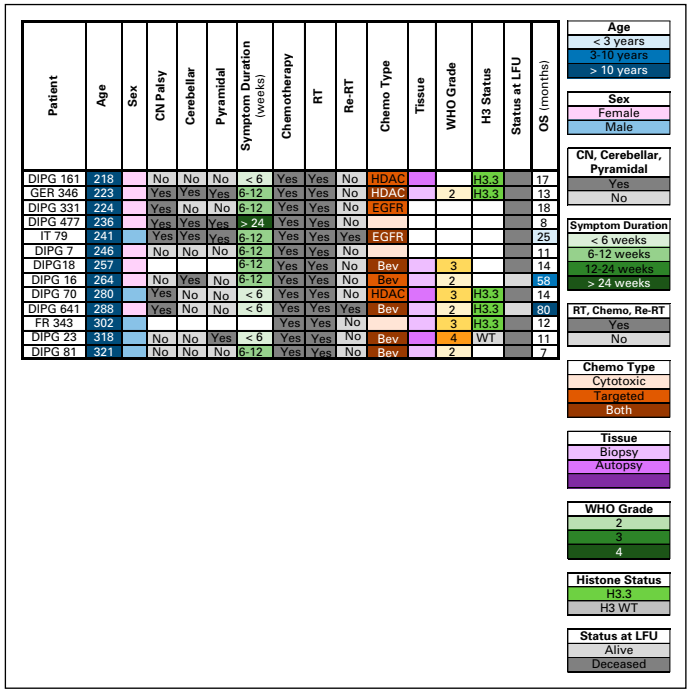


Fig A3. Clinical, radiologic, and molecular characteristics of patients with diffuse intrinsic pontine glioma age > 18 years. Bev, bevacizumab; CN, cranial nerve; DIPG, International DIPG Registry; EGFR, epidermal growth factor; FR, France; GER, Germany, Switzerland, Austria; HDAC, histone deacetylase inhibitor; IT, Italy; LFU, last follow-up; OS, overall survival; Re-RT, reirradiation; RT, radiation therapy; WT, wild type.

Table A1. Biopsies and Autopsies Performed by Country or Region

Country	No./Total No. (%) Biopsy	Autopsy
SIOPE-DIPGR		
France	109/113 (96)	2/115 (2)
Germany/Switzerland/Austria	81/278 (29)	4/16 (25)
The Netherlands	29/114 (25)	10/113 (9)
Italy	17/79 (22)	0/71 (0)
Croatia	2/7 (29)	0/5 (0)
United Kingdom	7/43 (16)	0/43 (0)
IDIPGR		
United States/Canada/Australia	54/372 (15)	61/376 (16)

Abbreviations: IDIPGR: International Diffuse Intrinsic Pontine Glioma Registry; SIOPE-DIPGR, European Society for Pediatric Oncology Diffuse Intrinsic Pontine Glioma Registry.

Table A2. Clinical, Radiologic, and Molecular Characteristics of Patients With Primitive Neuroectodermal Tumor

Patient	Age (months)	Symptom Duration (weeks)	Symptoms	Treatment at Diagnosis	OS (months)	Source of Tissue	Molecular Findings
DIPG-0051	27	Unknown	Unknown	RT + vorinostat	6	Biopsy	WT H3.3
DIPG-0165	53	< 6	CN, pyramidal	RT + vorinostat	7	Biopsy	WT *PDGFRA* and *EGFR*
DIPG-0236	62	< 6	Unknown	RT	5	Autopsy	Mutant *TP53* and *NF1* Amplified *MYCN* WT H3.3, H3.1, *ACVR1, PDGFRA, EGFR, ATRX, DAXX, PIK3CA, MET, CDKN2A/B, CCND1/2, CDK6, PPM1D*

Abbreviations: CN, cranial nerve; DIPG, International DIPG Registry; OS, overall survival; RT, radiation therapy; WT, wild type.