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Characteristics of patients ≥10 years of age with diffuse intrinsic pontine glioma: a report from the International DIPG/DMG Registry

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Abstract

Background. Diffuse intrinsic pontine gliomas (DIPG) generally occur in young school-age children, although can occur in adolescents and young adults. The purpose of this study was to describe clinical, radiological, pathologic, and molecular characteristics in patients ≥10 years of age with DIPG enrolled in the International DIPG Registry (IDIPGR).

Methods. Patients ≥10 years of age at diagnosis enrolled in the IDIPGR with imaging confirmed DIPG diagnosis were included. The primary outcome was overall survival (OS) categorized as long-term survivors (LTS) (≥24 months) or short-term survivors (STS) (<24 months).

Results. Among 1010 patients, 208 (21%) were ≥10 years of age at diagnosis; 152 were eligible with a median age of 12 years (range 10-26.8). Median OS was 13 (2-82) months. The 1-, 3-, and 5-year OS was 59.2%, 5.3%, and 3.3%, respectively. The 18/152 (11.8%) LTS were more likely to be older ($P < .01$) and present with longer symptom duration ($P < .01$). Biopsy and/or autopsy were performed in 50 (33%) patients; 77%, 61%, 33%, and 6% of patients tested had H3K27M (*H3F3A* or *HIST1H3B*), *TP53*, *ATRX*, and *ACVR1* mutations/genome alterations, respectively. Two of 18 patients with IDH1 testing were *IDH1*-mutant and 1 was a LTS. The presence or absence of H3 alterations did not affect survival.

Conclusion. Patients ≥10 years old with DIPG have a median survival of 13 months. LTS present with longer symptom duration and are likely to be older at presentation compared to STS. *ATRX* mutation rates were higher in this population than the general DIPG population.

Key Points

1. Individuals ≥10 years old with DIPG have a median survival of 13 months and over 10% of this cohort will have a survival of more than 2 years.
2. Long-term survivors are more likely to have older age and longer symptom duration.
3. *ATRX* mutation rates were higher in this population than the general DIPG population.

Importance of the Study

Previous studies of patients with DIPG have suggested that patients ≥10 years old have longer overall survival. This study investigates clinical, imaging, and biological characteristics of 152 individuals with image-defined DIPG that are ≥10 years of age at diagnosis. Median survival was 13 months and more than 10% of patients were alive ≥24 months from diagnosis. Older age and longer symptom duration to presentation were associated with LTS. In 50 patients with tissue available for histologic and biologic evaluation, the presence or absence of H3K27M was not significantly related to survival.

Diffuse intrinsic pontine gliomas (DIPG) comprise 80% of all childhood brainstem gliomas and are a leading cause of CNS tumor deaths in children, with a median survival <1 year.[1,2] Long-term survival of patients with DIPG (defined as overall survival [OS] >2 years) occurs in ≤10% of patients.[3] Characteristics that might contribute to a longer survival include younger age (<3 years at diagnosis), longer symptom latency, the absence of ring enhancement at diagnosis, and lack or presence of an *H3F3A* or *HIST1H3B* mutation, respectively.[4–8] Despite some reports that the use of adjuvant chemotherapy may improve survival, most studies have not demonstrated a significant difference, and focal radiotherapy remains the standard of care.[5,9]

Older age at diagnosis has previously been shown to portend a longer OS. In a phase II study using temozolomide and radiation therapy (RT), the authors noted that the group of patients who survived longer than 24 months had an older median age at diagnosis (13.6 years, range 9-18) than other DIPG patients.[10] Also, a large study from the International DIPG Registry (IDIPGR) in combination with the European Society for Pediatric Oncology DIPG Registry (SIOPE-DIPGR) demonstrated in DIPG patients who were >10 years old at diagnosis were more likely to be long-term survivors in multivariable analysis.[3] Variables that might impact survival for patients >10 years old have not been detailed. Although work has been completed to assess DIPG in adult patients, these studies include other entities besides imaging-defined DIPG or do not include older children.[11–14] It is unclear what characteristics may contribute to survival of this cohort of older children and adults with DIPG and further assessment is necessary. Using data from the IDIPGR we sought to define the clinical, radiologic, pathologic, and genetic/molecular characteristics of this cohort and how these variables may influence survival.

Materials and Methods

This was a retrospective registry analysis of patients enrolled in the IDIPGR. The infrastructure and methodology of the IDIPGR have been described elsewhere.[15] Relevant records were available as of April 9, 2019 (1010 patients).

Eligible patients included those ≥10 years of age at diagnosis and enrolled in the IDIPGR with centrally reviewed magnetic resonance imaging (MRI). Patients must have received radiation therapy and must have a known date of death or at least 24-months follow-up. Patients with characteristic DIPG by imaging appearance were included, while those with imaging where an alternative diagnosis was suspected were excluded from further analysis. Tumors with a histologic diagnosis of pilocytic astrocytomas were also excluded. The study was approved by the institutional review board at Cincinnati Children's Hospital Medical Center (CCHMC) after initial approval from the International DIPG Registry Advisory Committee for scientific merit.

Covariates of Interest

Clinical data were abstracted using standardized case report forms from the IDIPGR (C.E. and B.C.).[15] OS was defined as the time from diagnosis to death or last follow-up if survival was ≥24 months. OS was the primary outcome used in the assessment. Short-term survivors (STS) and long-term survivors (LTS) were defined as having OS times of <24 or ≥24 months, respectively. The value of 24 months to determine STS or LTS was chosen as an arbitrary cutoff in agreement with previous literature as fewer than 10% of patients generally survive >2 years from diagnosis.[3,4]

Demographic/clinical variables abstracted included age at diagnosis, gender, race, symptom duration before presentation, signs at presentation including cerebellar, pyramidal, and cranial nerve signs, and treatment with chemotherapy before disease progression.

For radiologic variables, MRIs were centrally reviewed and agreed upon by 2 neuroradiologists (J.L. and B.V.J.). Tumors were classified as (i) characteristic DIPG by imaging appearance (arises from the pons, exhibits a diffuse pattern of involvement, and involves ≥50% of the pons); (ii) likely DIPG with some unusual features (most commonly large areas of necrosis or hemorrhage) but otherwise characteristic of DIPG; or (iii) non-DIPG, alternative diagnosis suspected (which were excluded from further analysis). In those subjects with available MRI at diagnosis, imaging variables assessed were the presence of hemorrhage, necrosis, diffusion restriction, hydrocephalus, enhancement, ring enhancement, the extent of extrapontine tumor, tumor location, and tumor size.[16] Tumor size was documented by anterior-posterior (AP), transverse (TR), and craniocaudal (CC) measurements as detailed previously.[12] An estimated tumor volume was calculated using an ellipsoid model (volume = $4/3\pi$ [AP × TR × CC]). If an MRI scan at diagnosis was not available (n = 28), MRI during therapy was evaluated and these patients were included in the study based upon whether they were characteristic DIPG or likely DIPG

by central imaging review but were not analyzed for additional imaging variables.

Histology was defined according to the 2016 criteria, except in those cases where diagnostic tissue was collected before the implementation of the 2016 WHO criteria and not available for central review.[17,18] Genomic data were assessed using whole-genome sequencing, RNA sequencing, or clinical genomics panels. When more extensive sequencing was not feasible, Sanger sequencing was conducted to assess *H3F3A* (H3.3) or *HIST1H3B* (H3.1) mutations. In cases of limited tissues where sequencing was not possible, H3K27M and *TP53* mutations were assessed via immunohistochemistry (IHC) by pathology at CCHMC (C.F.). Mutations in *H3F3A* (H3.3) or *HIST1H3B* (H3.1) were considered mutually exclusive. Neither H3K27me3 status nor *EZHIP* overexpression was assessed in this cohort.

Statistical Analyses

Patient characteristics for clinical, radiographic, and biologic variables were summarized using frequencies and percentages or median and interquartile ranges. These statistics were also used to describe the patients who were excluded based on radiographic review. When comparing LTS and STS cohorts, variables were assessed using Fisher exact tests for categorical variables, while continuous variables were tested using the Wilcoxon rank sum test. OS was estimated using the Kaplan-Meier method. A Cox regression was not completed due to missing variables of >15% for 3 of 5 variables of interest (available data; age at diagnosis 100%, symptom duration 95%, tumor volume 79%, tumor necrosis 78%, ring enhancement 56%). Statistical evaluation was performed using SAS (Version 9.4). $P < .05$ was considered significant.

Results

Study Cohort

There were 208 patients ≥10 years of age identified, with 152 found eligible (Figure 1). Reasons for exclusion were (i) lack of imaging available for central review (n = 28), (ii) excluded by central radiology review (n = 18), (iii) did not receive radiation therapy (n = 3), (iv) date of death unknown or patient remains alive but for <2 years (n = 6), histology exclusion as pilocytic astrocytoma (n = 1, also excluded on central imaging review). The most common reason for imaging exclusion was that the tumor was not primarily in the pons 11/18 (61%). Three of 18 were not diffuse tumors (ie, focal and/or exophytic), 2/18 did not have diagnostic scans available or posttreatment changes made imaging interpretation unreliable, 1/18 was a suspected metastatic deposit possibly from a neuroendocrine tumor given findings of a positive octreotide scan, and 1/18 encompassed <50% of the pons. Of the 18 patients excluded by central imaging review, 10 patients (56%) had tissue diagnoses including high-grade glioma (5), diffuse glioma (1), pilocytic astrocytoma (1),

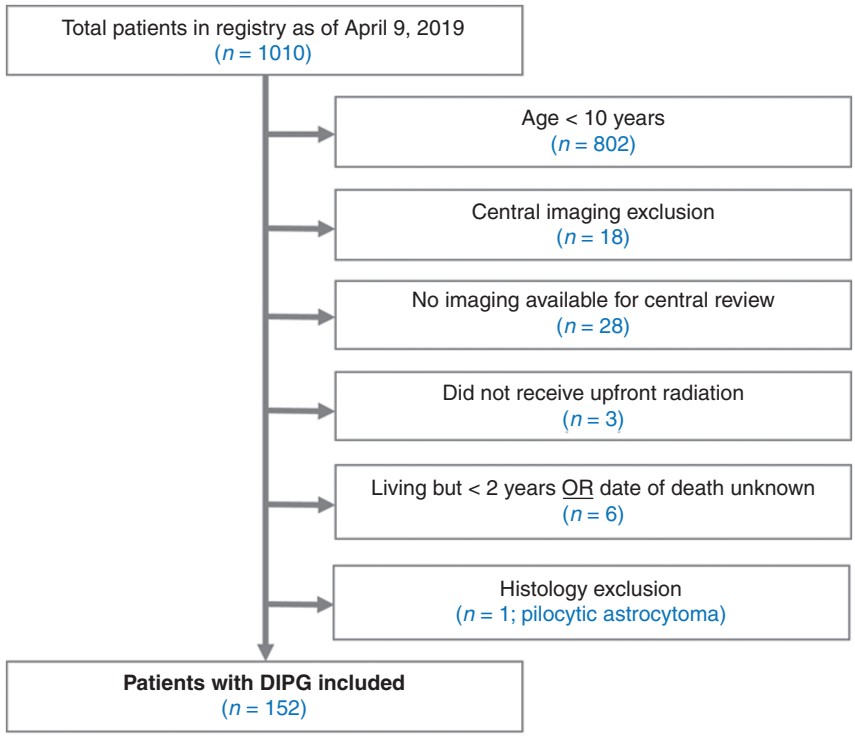

Fig. 1 Flowchart of patients excluded from the study.

gliosis/reactive changes (1), low-grade glioneuronal tumor (1), and germinoma (1). The 5 high-grade gliomas were specifically excluded due to not being located primarily in the pons (n = 4), and post-op changes extensive making assessment of DIPG vs non-DIPG not possible (n = 1).

Eighty-four of the 152 patients have been included in a previous publication.[3] One hundred twenty-four patients had imaging available at diagnosis and were used for imaging parameter assessments. The remaining 28 had available imaging at time points other than diagnosis and did not have additional imaging parameters evaluated.

The median age of the cohort was 12 years (range 10-26.8 years), 53% were male, and 28% of the cohort was >15 years. Cranial nerve symptoms were the most common presentation, followed by pyramidal and cerebellar signs or symptoms. The majority of patients received chemotherapy before relapse, and temozolomide was the most frequently delivered agent.

Imaging findings (% of cases) included: extrapontine extension (96%), enhancement (68%), diffusion restriction (64%), necrosis (31%), and hemorrhage (18%).

Pathologic diagnosis for the 50 patients with tissue details available from biopsy or autopsy showed that 32 (64%) were diagnosed using the WHO 2016 while the remainder were diagnosed using WHO 2007 or earlier. Available tissue details included 20 patients with local review only (15 with histology assessment only and 5 with limited molecular details), and 30 patients with central IDIPGR review (7 with IHC details, 6 with Sanger sequencing available for H3K27M, and 17 with whole-exome sequencing). Detailed description of clinical, imaging, histological and molecular variables are described in Table 1.

Survival

The median survival time of this study cohort was 13 months (interquartile range 9-18 months). The 1-, 3-, and 5-year OS rates were 59.2%, 5.3%, and 3.3%, respectively. Of the 152 patients that were included in the analysis, 18 (11.8%) were LTS. Kaplan-Meier curve for the entire cohort is shown in Figure 2A, while those for LTS and STS are shown in Figure 2B.

Comparison of Patient Characteristics Between LTS With STS

Clinical, radiographic, and biologic variables are compared and demonstrated in Table 2. LTS were more likely to be older ($P < .01$) and have a longer duration from symptom onset to presentation ($P < .01$). Imaging variables were not significantly different except for LTS having larger AP tumor diameters ($P = .024$). Tumor necrosis and ring enhancement were seen more frequently in STS compared to LTS (33% vs 8% and 35% vs 14%, respectively); however, these were not statistically significant ($P = .1$ and .19, respectively).

Somatic Genetic Alterations

Fifty patients (33%) had tissue available for molecular-pathologic analysis with autopsy, biopsy, or both completed in 29, 17, and 4 patients, respectively, including 6 LTS and 44 STS. However, tissue available through the registry for sequencing was limited. H3K27M mutation was the most frequent alteration, occurring in 27/35 (77%), followed by mutations in *TP53* 19/31 (61%) and *ATRX* 7/21 (33%). Neither the presence nor absence of an H3K27M mutation (*H3F3A* or *HIST1H3BC*) or *TP53* gene alteration was found to be associated with LTS vs STS, although numbers were limited (Table 2).

For the 6 of 18 LTS with tissue collected, 4 patients had H3K27 status assessed where 3 of 4 were H3 K27M-mutant. Only 2 of the 6 LTS had tissue available for further sequencing. Interestingly, somatic *NF1* mutations were found in both of the LTS tested but none of the 9 STS tested had somatic *NF1* mutations. Germline testing for *NF1* mutations was not completed in available patient samples. In addition, 1 of the 2 LTS assessed for *IDH1* was mutant and this patient was also H3WT. Although 44 STS had tissue available, extended sequencing was achievable only for a subset of these patients. A complete assessment of all genetic findings is shown in Figure 3 for both LTS and STS.

Discussion

This study is a large assessment directed at patients ≥10 years of age with DIPG and includes 152 patients. OS appears to be slightly longer in patients ≥10 years of age with a median survival of 13 months compared to 9-11 months from other large published cohorts.[2,6,19] These data also support other studies suggesting that older age portends a slight survival advantage.[10,16] Our LTS frequency of 11.8% is similar to that previously reported for patients ≥10 years of age (13.9%), which was statistically higher than those <10 years old of 8.9%.[3] Furthermore, this cohort of patients ≥10 years of age have a 1-year OS of 59.2% which appears higher than other large studies including a systematic review reporting a 1-year OS of 41%.[20]

In general, the intersection between pediatrics and adults in neuro-oncology is poorly investigated. In adults, it is known that pontine gliomas behave differently from those in children and are more often low grade or non-diffuse in nature.[21] However, when specifically assessing H3K27M-mutant diffuse midline gliomas (DMG) in adults (≥18 years) a median OS of 19.6-27.6 months has been demonstrated.[11,12] However, the majority of adult H3K27M-mutant DMG occur in the diencephalon with only approximately 5%-8% occurring in the pons. When specifically analyzing image-defined diffuse intrinsic brainstem gliomas in adults, Reyes-Botero et al reported on 11 patients with high-grade glioma histology who had a median OS of 16 months, although several tumors were not primarily pontine-based.[13] These patients had histology grade 2-4 and molecular assessment showed 3 of 8 (38%) tested tumors had histone mutations, while 3 of 17 (17%) had *IDH1* mutations detected via IHC or Sanger sequencing.[13] Similarly a study by Chen et al with 126 patients of all ages and Asian race with brainstem gliomas had 33 (26%) patients with tumors classified as DIPG.[14] Of the 31 DIPG patients with methylation data, 27 (87%) clustered with H3-pons while the remaining 4 had IDH clustering and were all >10 years of age with improved survival compared to those in the H3-pons cluster.[14] This study again illustrates

Table 1 Patient Characteristics (n = 152)

Demographic/Clinical		Frequency (%)
Age, median in years (range)	12.2 (10.0-26.8)	
Age greater than 15 years old	42	28
Gender, male	81	53
Race		
Caucasian	77	74
African descent	7	7
Asian	5	5
Other	16	15
Symptom duration prior to presentation		
<6 weeks	88	61
6-12 weeks	33	23
12-24 weeks	15	10
>24 weeks	8	6
Symptoms at presentation		
Cerebellar, present	78	60
Pyramidal, present	51	40
Cranial nerve, present	90	70
Treatment		
Re-irradiation, yes	12	8
Chemotherapy prior to first progression, yes	106	72
Chemotherapy anytime, yes	124	87
Chemotherapy type		
Targeted	40	32
Cytotoxic	38	31
Both target and cytotoxic	46	37
Type of targeted therapy used		
EGFR inhibitor used	21	17
mTOR or PI3K inhibitor used	14	11
HDAC inhibitor used	22	18
VEGF inhibitor used	31	25
Vaccine	3	2
Convection enhanced delivery	4	3
Temozolomide used	52	42
Imaging parameters (at diagnosis, n = 124)		
Tumor volume (cm^3)	301 (216-421)	—
Extrapontine extension, yes	120	96
Eccentric tumor present	20	16
Hemorrhage present	21	18
Diffusion restriction, any	68	64
Enhancement, any	77	68
Necrosis, any	36	31
Ring enhancement, present	28	33
Hydrocephalus, present	17	15
Distant metastases	2 of 55 (only 15 with spine imaging)	4

Table 1 Continued

Tumor tissue available/histology		
Received autopsy and/or biopsy		
Autopsy	29	19
Biopsy	17	11
Both autopsy and biopsy	4	3
Neither autopsy or biopsy	102	67
Histomolecular information		
Local institution review with histology only	5	10
Local institution with limited molecular details	15	39
Central review with IHC	5	19
Central review with Sanger sequencing	6	12
Central review with WES	19	38
WHO tumor grade		
2	3 (1 H3WT; 2 H3 not assessed)	6
3	9 (3 H3WT; 6 H3 not assessed)	18
4 (histology only)	10 (3 H3WT; 7 H3 not assessed)	20
4 (H3K27M)	27	55

Abbreviation: IHC, immunohistochemistry; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; VEGF, vascular endothelial growth factor; WES, whole exome sequencing.

the need to consider genomic assessment in older patients as *IDH1* mutant tumors can have a classical DIPG imaging appearance which portends an improved prognosis. The histone mutation frequency in our cohort was 77% of those tested; however, this is not directly comparable to methylation data. *IDH1* mutations in pediatric gliomas are found to occur mainly in children older than 14 years of age. In our cohort, 2 of 18 patients tested for the *IDH1* mutation in our cohort were found to have *IDH1* mutant tumors and 1 was an LTS of 33-month duration. Our findings, as well as previous findings of IDH1 mutations in DIPG, suggest that this testing should be considered in older patients with DIPG, especially those without H3K27M mutation, as these mutations are mutually exclusive.[22–24]

Somatic *NF1* mutations were found in both of the LTS tested for the alteration and none of the 9 STS tested. These patients were 22.0 and 24.0 years old at diagnosis, with survival times of 78 and 82 months, respectively. MacKay et al show, of 322 DIPG tumors, 7 had *NF1* alterations with an estimated median age and survival of 10 years and 9 months.[6] Also, 2 other studies found *NF1* alterations in 13 of 63 high-grade brainstem tumors (3 of 33 DIPG) with a median age of 27 years and in 7 of 20 adult H3K27M-mutant DMG.[12,14] These publications suggest that somatic *NF1* alterations do not influence survival in DIPG but might occur at a higher frequency in older individuals. It is possible that, in our cohort, the *NF1* mutations coincidentally occurred only in LTS due to low numbers and further investigation is warranted. In addition, germline *NF1* testing was not complete in these patients.

Previously, large analyses of DIPG patients of all ages have been completed. Importantly, Hoffman et al assessed both SIOPE-DIPGR (n = 634) and the IDIPGR (n = 374) for a total of 1008 patients. Their study showed that LTS were more likely to be >10 or <3 years old at diagnosis, receive systemic therapy at diagnosis, have longer symptoms duration, and less likely to have cranial nerve palsies or ring enhancement, necrosis, or extrapontine extension on diagnostic MRI than STS.[3] Our study represents patients solely from the IDIPGR and none from the SIOPE registry. Since the Hoffman et al's study, the IDIPGR has now more than doubled in size to 1010 patients. For patients ≥10 years of age, this cohort adds an additional 7 LTS and 61 STS with updated clinical, radiographic, and biologic data. Compared to Hoffman et al's cohort of all ages, patients ≥10 years of age often have a longer symptom duration to presentation with 39% having more than 6 weeks of symptoms before diagnosis compared to 33%. Those ≥10 years of age are less likely to present with cranial nerve palsies (70% vs 82%), pyramidal tract signs (40% vs 51%), or necrosis (31% vs 40%) on diagnostic imaging. Suggesting that in addition to survival there are clinical factors more common at presentation in this older age group warranting further exploration.

DIPG biology has been extensively assessed in the past several years.[6–8] In our biology sample from 50/152 patients, varying amounts of tissue were available to the IDIPGR for analysis. This largely depended on molecular details shared or the availability and viability of tissue sent from the patient's primary institution. No differences were appreciated between LTS and STS concerning *H3F3A*, *HIST1H3*, or WT status. This is in contrast to previous findings[7] where patients with *HIST1H3B/C* were found to have significantly longer survival. This discordance with published literature is likely in part due to the small biology sample size in our cohort, especially limited in *HIST1H3*-altered tumors. Despite *HIST1H3* mutations being more common in younger children with DIPG,[3,7]

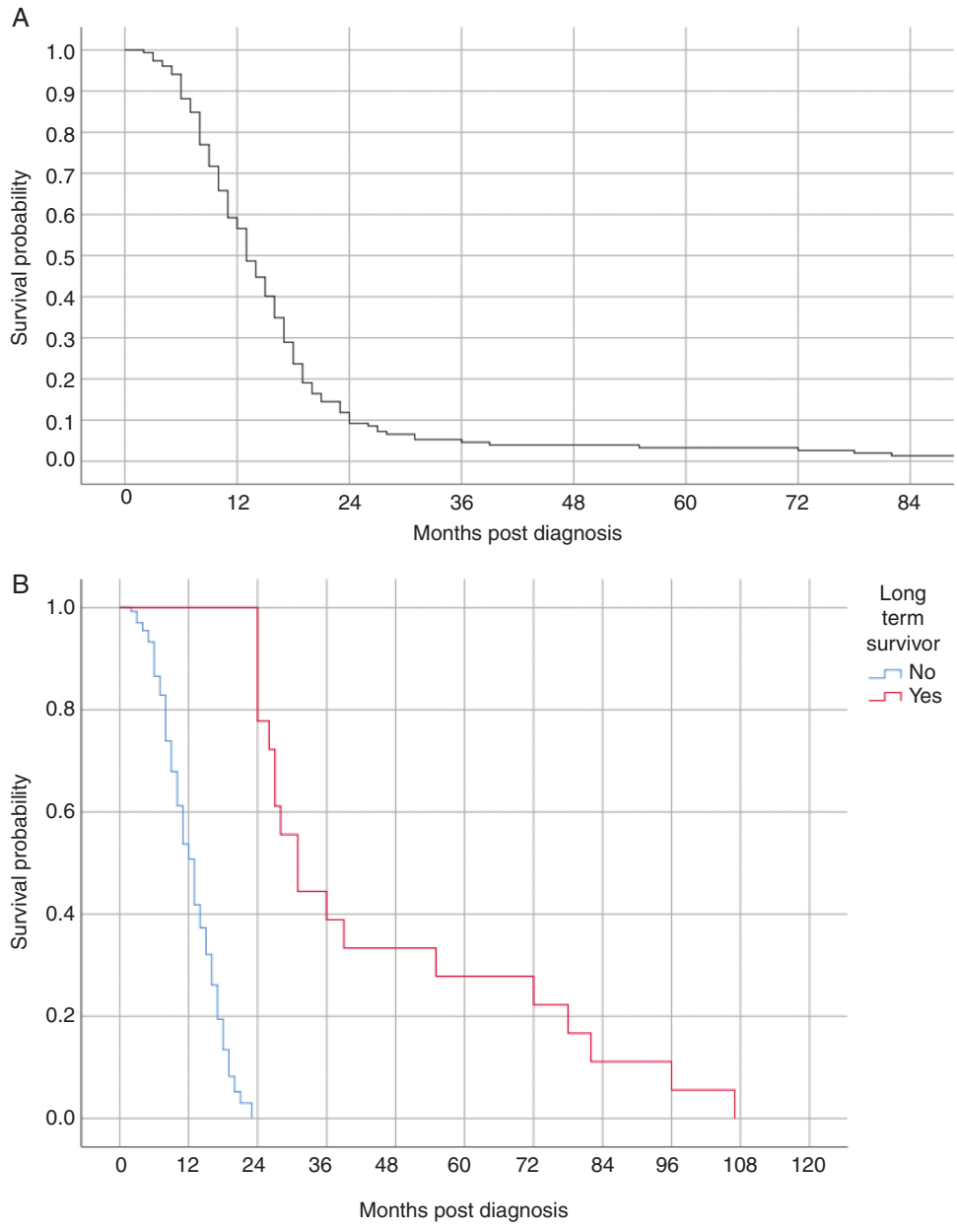

Fig. 2 Kaplan-Meier plots for overall survival. (A) Entire Cohort ≥10 years of age. (B) Long-term survivors and short-term survivors.

patients in our cohort were still found to harbor this mutation but at a lower frequency than seen in younger children.

Recent work by Castel et al shows a cohort of H3WT DIPG that show upregulation of *EZHIP* and often have co-occurring mutations in *ACVR1*, *PIK3CA*, *PIK3R1*, and *PTEN*. These *EZHIP* overexpressed tumors were also found to have an older median age of 10 years with longer survival, akin to H3.1-mutated tumors generally seen in young children. Although *EZHIP* overexpression was not assessed in our cohort, there were 8 known H3WT in our biology cohort of 35 patients tested (23%) with a median age of 19.4 years, although only 1 of 8 was an LTS.

ACVR1 mutations have been previously reported in 32% of DIPG patients, but in this cohort was found in only 1 of 18 (6%) of patients in our cohort. The frequency in our cohort is low, potentially due to its known high association with *HIST1H3B* and younger age. *TP53* mutations were present in 61% of tumors in our cohort and similar to other genomic studies on DIPG, this mutation was commonly co-expressed in tumors with *H3F3A* mutations and absent from tumors with *HIST1H3* mutations. *ATRX* mutations occur in DIPG at frequencies of 9%-11% but occurred in 7 of 21 (33%) of our patients which has previously been associated with older age in DIPG, other pediatric cancers including neuroblastoma,

Table 2 Univariable Analyses Comparing Clinical, Radiologic, and Pathologic Characteristics of LTS and STS in Patients ≥10 Years of Age

Characteristic	LTS (n = 18)	STS (n = 134)	*P*
Clinical			
Age	15 (12-16)	12 (11-15)	<.01
Race			.24
African descent	2	5	
Asian	1	4	
Caucasian	9	68	
Other	0	16	
Gender			.19
Male	7	74	
Female	11	60	
Symptom duration			<.01
<6 weeks	4	84	
6-12 weeks	10	23	
12-24 weeks	2	13	
>24 weeks	2	6	
Chemotherapy prior to progression			.53
Yes	15	91	
No	3	38	
Repeat irradiation			.13
Yes	3	9	
No	13	120	
Symptoms at presentation			
Cranial nerve palsy			.69
Yes	10	80	
No	6	33	
Pyramidal tract signs			.41
Yes	4	47	
No	12	65	
Cerebellar signs			.52
Yes	10	68	
No	7	45	
Imaging at presentation			
Median tumor size, mm (range)			
Anteroposterior (AP)	41 (35-43)	35 (32-39)	.02
Transverse (TR)	50 (48-52)	46 (40-51)	.15
Craniocaudal (CC)	44 (38-53)	44(38-51)	.83
Volume cm^3 (range)	371 (253-491)	295 (216-407)	.13
Hemorrhage			.81
Yes	3	20	
No	11	88	
Necrosis			.1
Yes	1	36	
No	12	72	
Ring enhancement			.19
Yes	1	28	
No	6	51	

Table 2 Continued

Characteristic	LTS (n = 18)	STS (n = 134)	*P*
Hydrocephalus at presentation			.69
Yes	1	16	
No	13	88	
Biology			
H3K27 (molecular and/or IHC)			.72
Mutant	4	23	
WT	1	7	
H3F3A (molecular only)			.37
Mutant	1	15	
WT	2	5	
HIST1H3BC			.42
Mutant	1	2	
WT	2	20	
TP53			
Mutant	3	15	.57
WT	2	11	
NF1			
Mutant	2	0	.01
WT	0	9	

Abbreviations: IHC, immunohistochemistry; LTS, long-term survivors; STS, short-term survivors; WT, wild type.

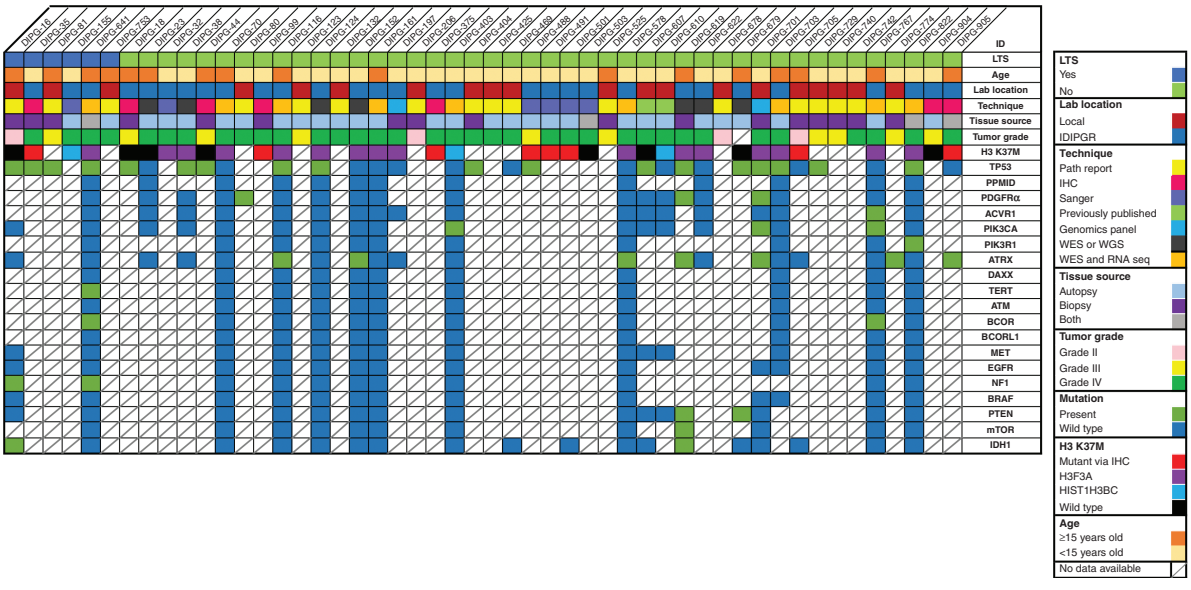

Fig. 3 Genetic alterations in patients ≥10 years old with DIPG. Abbreviation: DIPG, diffuse intrinsic pontine gliomas.

and adult patients with H3K27M-mutant DMG. In DIPG and other gliomas, alterations in *ATRX* are associated with slower tumorigenesis and improved survival which may partly explain their increased frequency in older patients and slightly longer survival, although patients nonetheless succumb to their disease.[25,26] The frequency of other mutations were found to be similar to previously-cited studies.

There were 18 LTS in this study. Clinically, LTS had a longer time from symptom onset to diagnosis. Larger AP tumor dimension at diagnosis was more common in the LTS cohort compared to STS, although TR and CC dimensions were not statistically different. Estimation of tumor volume (4/3π [AP × TR × CC dimensions]) did not have an impact on survival. A previous study has demonstrated that larger tumor volume before RT is associated with longer progression-free survival, while Hoffman et al showed that smaller CC measurement at baseline was associated with better survival.[3] Although there can be inter-observer variability in tumor measurements, the presented study had tumor measurements conducted by 2 neuroradiologists who review all tumors for the IDIPGR and have recently shown no statistical differences in their inter-rater measurement differences.[16]

DIPG is a diagnosis based on radiographic and clinical criteria, and it has been shown that central radiology review can alter the true diagnosis of DIPG by nearly 10%.[16] Of the 18 (11.8%) patients excluded based on central imaging review, only 2 patients were LTS and neither had tissue available for review. However, of the 9 excluded patients with available tissue, 2/9 (22%) tumors had WHO grade I histology, and another 2/9 (22%) were non-glial. The remaining 5 of these 9 patients had high-grade gliomas or diffuse gliomas. These pathologic findings highlight the importance of tissue diagnosis in cases with unclear radiologic findings to help guide management. Also, these findings speak to the importance of having a central radiographic review for patients with DIPG.

Limitations of this study include regression analyses were not appropriate due to the small number of LTS. In addition, some variables had >15% missing data which is a limitation of registry data analysis, making generalizations difficult. Six LTS in our study underwent either a biopsy or autopsy, while only 4 had tissue available for molecular testing. Although tissue was collected on about 1/3 of patients in this cohort (33%), the amount collected and methods of storing patient samples were heterogeneous. Not all patients with tissue collected were able to be analyzed with additional molecular investigation. Patients with WT H3K27 tumors were not assessed for H3K27me3 status nor *EZHIP* overexpression in this cohort and germline testing for *NF1* mutations was not assessed. DIPG tumor tissue is a valuable resource in the research community further limiting tissue sharing. The tissue analyzed in this study was based on standard-of-care collection which varies per institution and year of diagnosis. Importantly although LTS in this cohort is defined as those alive ≥24 months from diagnosis, all patients eventually succumb to their disease suggesting only slight delays in progression of disease compared to younger patients as our studies 3- and 5-year OS are similar to other published data.[4,20]

Conclusions

Patients ≥10 years old with DIPG have a median survival of 13 months and are LTS in 11.8% of cases. Those in the LTS cohort are likely to be older in age and present with longer symptom duration before diagnosis. Biologically, patients ≥10 years old with DIPG have high rates of *ATRX* and a low frequency of *ACVR1* mutations. *IDH1* mutation testing should be considered in older patients, especially in those who are WT H3K27. As we engage in gaining more tissue at diagnosis in this patient group, it will be important to continue ongoing clinical and radiographic correlation to stratify patients with DIPG.

Keywords

≥10 years old | DIPG | International DIPG Registry | outcomes

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