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MR imaging features of diffuse intrinsic pontine glioma and relationship to overall survival: report from the International DIPG Registry

James L. Leach, James Roebker, Austin Schafer, Joshua Baugh, Brooklyn Chaney, Christine Fuller, Maryam Fouladi, Adam Lane, Renee Doughman, Rachid Drissi, Mariko DeWire-Schottmiller, David S. Ziegler, Jane E. Minturn, Jordan R. Hansford, Stacie S. Wang, Michelle Monje-Deisseroth, Paul G. Fisher, Nicholas G. Gottardo, Hetal Dholaria, Roger Packer, Katherine Warren, Sarah E. S. Leary, Stewart Goldman, Ute Bartels, Cynthia Hawkins, and Blaise V. Jones

Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (J.L.L., J.R., B.V.J.); Department of Pathology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (C.F.); Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (A.S., J.B., B.C., M.F., A.L., R.Dou., R.Dri, M.D.S.); Kids Cancer Centre, Sydney Children's Hospital, Sydney, AU (D.S.Z.); Division of Oncology, Children's Hospital of Philadelphia, Pennsylvania (J.E.M.); Children's Cancer Centre, Royal Children's Hospital; Murdoch Children's Research Institute; University of Melbourne, Melbourne, Australia (J.R.H., S.S.W.); Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, California (M.M.D., P.F.G.); Department of Oncology, Perth Children's Hospital, Perth, AU (N.G.G., H.D.); Division of Oncology, Children's National Medical Center, Washington, DC (R.P.); Dana-Farber Cancer Institute, Boston Children's Cancer and Blood Disorders Center, Harvard Cancer Center, Boston Massachusetts (K.W.); Cancer and Blood Disorders Center, Seattle Children's, Seattle, Washington (S.E.S.L.); Division of Oncology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois (S.G.); Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, CA (U.B.); Division of Pathology, The Hospital for Sick Children, Toronto, CA (C.H.); Department of Neuro-oncology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands (J.B.); Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio (R.D.); Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, Ohio (J.L.L., J.R., B.V.J)

Corresponding Author: James L. Leach, MD, Professor of Radiology, Department of Radiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, 3333 Burnet Avenue Cincinnati, OH 45229 (james.leach@cchmc.org).

Abtract

Background. This study describes imaging features of diffuse intrinsic pontine glioma (DIPG) and correlates with overall survival (OS) and histone mutation status in the International DIPG Registry (IDIPGR).

Methods. Four hundred cases submitted to the IDIPGR with a local diagnosis of DIPG and baseline MRI were evaluated by consensus review of 2 neuroradiologists; 43 cases were excluded (inadequate imaging or alternative diagnoses). Agreement between reviewers, association with histone status, and univariable and multivariable analyses relative to OS were assessed.

Results. On univariable analysis imaging features significantly associated with worse OS included: extrapontine extension, larger size, enhancement, necrosis, diffusion restriction, and distant disease. On central review, 9.5% of patients were considered not to have DIPG. There was moderate mean agreement of MRI features between reviewers. On multivariable analysis, chemotherapy, age, and distant disease were predictors of OS. There was no difference in OS between wild-type and H3 mutated cases. The only imaging feature associated with histone status was the presence of ill-defined signal infiltrating pontine fibers.

Conclusions. Baseline imaging features are assessed in the IDIPGR. There was a 9.5% discordance in DIPG diagnosis between local and central review, demonstrating need for central imaging confirmation for prospective trials. Although several imaging features were significantly associated with OS (univariable), only age and distant disease were significant on multivariable analyses. There was limited association of imaging features with histone mutation status, although numbers are small and evaluation exploratory.

Key Points

1. Detailed description of baseline MR imaging features currently evaluated in the IDIPGR.
2. Multiple imaging features correlated with OS.
3. There was limited correlation with H3K27M mutation status.

Importance of the Study

This study represents a detailed description of baseline MR imaging features currently evaluated in the IDIPGR, which will serve as a guide for imaging definitions and a resource for future IDIPGR approved research projects. While some imaging features correlated with OS, there was more limited correlation with H3K27M mutation status (although numbers are small).

Brainstem tumors make up 10–20% of central nervous system tumors in children and are traditionally divided into tumors that are focal and well defined (20%) or diffuse (80%) on imaging.[1,2] Prognosis for diffuse brainstem tumors has remained very poor.[1] Recently, the discovery of recurrent somatic gain-of-function mutations leading to lysine 27 to methionine (p.Lys27Met,K27M) substitution in histone 3 (H3) variants (H3.3 and H3.1) in approximately 80% of diffuse brainstem tumors has transformed our understanding of their biology.[3–5] Initial reports indicated patients with H3K27M-mutant tumors have a worse prognosis than wild-type (WT) diffuse brainstem tumors, despite similar histopathology (World Health Organization [WHO] grades II–IV astrocytomas).[3,6] This has led the WHO to reclassify pediatric diffuse gliomas into a newly defined entity, "diffuse midline glioma, H3K27M–mutant," which includes tumors of the brainstem, spinal cord, and thalami.[7] The term "DIPG" remains relevant as a clinical-radiologic diagnosis encompassing diffuse tumors intrinsic to the pons, many (but not all) of which will be H3K27M-mutants.[6] Despite these advances, imaging genomic correlations are few.[6,8]

Imaging is critical to establish a probable diagnosis of DIPG, define extent of disease, exclude other diagnoses, and guide biopsy when indicated.[9] Prior studies have related imaging findings to survival with variable results.[2,9–12] Part of this variability is likely related to differing imaging criteria for DIPG, different definitions for key imaging features, lack of standardization of sequence acquisition, small numbers of subjects, as well as inclusion of focal and exophytic tumors.[13,14]

In order to improve our understanding of these devastating tumors, we and our European colleagues have established multi-institutional registries.[15,16] To date, the International DIPG Registry (IDIPGR) has enrolled 1032 patients from 115 participating institutions in 15 countries. Limited imaging results on 247 subjects in the IDIPGR cohort have been recently reported as part of a validation dataset of a prognostic model initially assessed in the European Society for Paediatric Oncology (SIOPE) DIPG cohort.[17] The current study reports an analysis of the full imaging features available in the IDIPGR.

Materials and Methods

This study was approved by the scientific review board of the IDIPGR and the local institutional review board at Cincinnati Children's Hospital Medical Center. Details of recruitment and structure of the IDIPGR have been described previously.[15] All submitted cases as of July 2018 with centrally reviewed baseline MR imaging were eligible for inclusion. Clinical information included: age, sex, symptom duration, neurologic findings, treatment with any chemotherapy, treatment with radiotherapy, and duration of related symptoms before diagnosis.

Imaging Review

Imaging evaluation was performed blinded to clinical data, as previously described.[15] MR imaging studies were reviewed by both registry neuroradiologists (26 and 25 years of post-fellowship clinical experience) utilizing a referenceable nomenclature. One reviewer would assess the case and fill out a standardized form. The second reviewer would then assess the case, referencing the form from the primary reviewer. Consensus opinion was utilized if there were discrepancies between reviewers and all imaging features were assessed and agreed upon by both reviewers. Imaging features were defined based in part on prior imaging studies of DIPG[2,11–13,18–20] optimized for reproducibility by assessment of an initial 20 learning cases by both reviewers (subsequently reevaluated as part of the final imaging review process). For the last 30 evaluated subjects, imaging features were assessed by both reviewers independently to define interobserver variability. For the first 30 evaluated subjects, tumor and pons measurements were performed separately by both reviewers for purposes of defining interobserver variability. For the remainder, tumor and pons measurements were performed by one reviewer and checked by the other reviewer, and consensus measurements made if there were discrepancies.

Each case was categorized by the neuroradiology reviewers as: (i) characteristic DIPG by imaging appearance (arises from the pons, exhibits a diffuse pattern of involvement, and involves ≥50% of the pons)[2,11]; (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)[20–22] (Supplementary 1). Excluded for the purposes of this study were cases in which there was secondary brainstem involvement by a tumor centered in the thalami, cerebral hemispheres, or cerebellar hemispheres.

Imaging features were visually evaluated (Supplementary 1) including: tumor size by linear measurement, pons dimension, extension, percent of pons involved (cross-sectional area on any cut over the pons, subjectively assessed), eccentric position, tumor margin, signal intensity, heterogeneity, localized T2 hypointensity,[23] diffusion restriction, hemorrhage, enhancement characteristics, necrosis, tumor perfusion, spectroscopic features, hydrocephalus, and presence of distant noncontiguous disease (intracranial and intraspinal). Other imaging features were assessed in an exploratory manner to correlate with biologic data and were not part of the registry core imaging features described above (Supplementary 2). These included the presence of "stripes" (previously described by Castel et al)[6] nonnecrotic T2 hyperintensity regions,[19] as well as the presence of diffuse T2 fluid attenuated inversion recovery hypointensity within the tumor (a pattern recognized during our review of cases for this study). Quantitative analysis of diffusion, perfusion, and spectroscopy data was not undertaken in this study due to the limited and variable nature of the submitted sequences.

Histone Mutation Status

Subjects ($n = 57$) had biologic data from biopsy or autopsy. In addition to histologic diagnosis, genomic data were derived from whole genome sequencing, whole exome sequencing, RNA sequencing, or clinical genomics panels and mutation status of loci for *H3F3A* (H3.3), *HIST1H3B* (H3.1), or immunohistochemistry (IHC) assessment of histone mutation status by report supplied by each institution or through tissue re-staining. The IHC method utilizes a polyclonal mutant-specific antibody that recognizes the product of all H3K27M variants (including H3.3, H3.1, and others), a positive result visualized microscopically as strong nuclear staining of the tumor cells.[18]

Statistical Analysis

Univariable and multivariable analyses of imaging features, clinical data, and histone status relative to overall survival (OS) (diagnosis to death) were performed using Cox proportional hazards regression. Results were summarized for OS and histone status with a hazard ratio (HR) and an odds ratio (OR), respectively. Features with $P < 0.05$ in univariable analysis were chosen for multivariable analysis when applicable. Agreement between reviewers was assessed with concordance rates and kappa statistics for imaging features, and paired *t*-tests for quantitative data.

Results

Excluded Cases

A total of 400 cases with baseline imaging available as of September 2018 were reviewed. Of these, 43 (11%) were excluded from further analysis: 5 no baseline MRI, 22 nonpontine origin, and 16 with imaging features strongly suggestive of another diagnosis. These included well-defined exophytic tumors with marked enhancement (likely pilocytic, $N = 7$), localized, markedly diffusion restrictive, often eccentric tumors (presumed primitive neuroectodermal tumor, $N = 5$), diffuse or multifocal tumors with primarily hemispheric and thalamic involvement with secondary brainstem extension ($N = 2$), and lesions with ill-defined minimal signal (presumed nonneoplastic, $N = 2$) (Supplementary 1). Thus, 38/400 subjects (9.5%) with a local diagnosis of DIPG did not meet imaging criteria for DIPG based on central review.

Demographic, Clinical, and Imaging Details

Of the 357 patients with a clinical-radiologic diagnosis of DIPG, 197 were females, 160 males. Median age was 6.2 years (range, 1 mo–27 y). $N = 272$ (76%) subjects received chemotherapy, and 336 (94%) radiotherapy (267 both; 61 only radiotherapy, 4 only chemotherapy, 12 neither, 8 radiotherapy—unknown chemotherapy status, 1 chemotherapy, unknown radiotherapy status, 4 unknown treatment status). Studies ($n = 347$) incorporated administration of a gadolinium-based contrast agent, 292 studies included diffusion sequences, 146 studies included gradient recalled echo (GRE) or susceptibility weighted imaging (SWI) sequences, 31 studies included perfusion imaging, and 88 studies included spectroscopy within the tumor. Baseline spine studies were available for review in 133 cases.

Interobserver Agreement

On central review, there was no significant difference in tumor measurements between reviewers (Table 1). There was a significant difference in anterior-posterior (AP) pontine measurements between reviewers with no significant difference in transverse (TR) pontine measurement (Table 1).

Using dichotomized MRI feature classifications, there was moderate mean agreement between reviewers (mean agreement rate, 0.838; mean kappa, 0.622), with some variability (Table 2).

MRI Features of DIPG

A summary of the MRI features is given in Table 3: 11 had distant non-contiguous tumor at diagnosis (3.1%; 6.8%

in those with spine imaging at baseline), including intracranial leptomeningeal (n = 5, 1.4%), spinal leptomeningeal (n = 5, 1.4%), subventricular[24] (n = 2, 0.6%), cerebellar parenchymal (n = 1), spinal parenchymal (n = 1), noncontiguous midbrain and thalamus (n = 1). Four cases had mixed patterns. Of 133 subjects with baseline spine imaging, 4 (3%) had spinal distant disease (1 cervical cord, 3 leptomeningeal), with 2 (1.5%) as their only distant disease site. Overall, 6 (1.7%) cases had spinal and 8 (2.2%) had intracranial disseminated disease at diagnosis.

MRI Features and Overall Survival

OS data were available for 351 cases (median survival, 10.9 mo; range, 0.1–100.5 mo, 1 alive at time of data collection). On univariable analyses, clinical and imaging features that significantly correlated with shorter OS included (Table 4): shorter symptom duration, no chemotherapy, tumor extension into the midbrain and/or beyond pons and brachium pontis, larger cranial-caudal (CC) tumor dimension, larger AP × CC tumor product, larger AP tumor/pons measurement ratio, presence of diffusion restriction, tumor enhancement or necrosis, and presence of distant disease at diagnosis. A full listing of assessed features is given in the Supplementary Material (Supplementary 3). On multivariable analysis shorter symptom duration and distant disease at diagnosis remained significantly correlated with shorter OS (Table 5).

Table 1 Interobserver agreement, tumor and pons measurements

Measurement	Mean Difference (mm)	Range	*P*
Tumor AP	2.6 mm	0–15 mm	0.155
Tumor Trans	3.7 mm	0–17 mm	0.604
Tumor CC	2.5 mm	0–41 mm	0.139
Pons AP	1.8 mm	0–6 mm	***0.0001***
Pons Trans	1.8 mm	0–5 mm	0.065

Histone Status

As an exploratory analysis, 57 subjects with available histone mutation status (detailed above) were assessed: 17 had analysis by IHC (7 had only IHC for histone status) and 50 had genomic data. In those with genomic data available, 29 cases were H.3, 11 cases were H.1 mutated, and 10 were WT (Table 6). Because of the small numbers of subjects, histone status was pooled and classified as: H3 mutation positive (either IHC positive, HIST1H3B (H3.1) positive, or H3F3A (H3.3) positive], or WT (IHC negative, without H3.3 or H3.1 mutations on genomic assessment). Using this classification, there were 47 H3 mutation subjects and 10 WT subjects. There was no difference in OS between (i) H3 mutation and WT subjects (HR 0.97, P = 0.927) or between (ii) those with H3.3 or H3.1 histone status (HR 1.22 for H3.3, 1.0 for H3.1, P = 0.583), although numbers were

Table 2 Interobserver agreement of MRI feature classification*

Feature	N	Agreement Rate	Kappa (UW, Observed)	Kappa (max)
Tumor extension beyond pons/BP	30	0.830	0.210	0.526
Tumor extension (raw)	30	0.330	NA	NA
Tumor margins (well vs ill-defined)	30	0.800	NA	NA
Tumor location (central vs eccentric)	30	0.930	0.634	0.634
Tumor extent (contained vs exophytic)	30	0.767	0.420	0.420
Tumor signal (T1/T2)	30	1.000	1.000	1.000
T2 hypointensity	30	0.533	0.110	0.237
Diffusion restriction	18	0.778	0.517	0.753
Heterogeneity (any)	30	1.000	1.000	1.000
Heterogeneity (raw)	30	0.667	NA	NA
Hemorrhage	30	0.933	0.634	0.634
Enhancement (yes vs no)	29	0.897	0.731	0.910
Enhancement pattern	29	0.758	0.638	0.774
Necrosis	30	0.933	0.864	1.000
Spectroscopy Cho elevation	7	0.570	NA	NA
Spectroscopy reduced NAA	7	0.860	NA	NA
Spectroscopy lactate	7	0.860	NA	NA
Hydrocephalus	30	0.967	0.911	0.911
Non-DIPG	30	0.967	NA	NA
Mean (dichotomized)		**0.838**	**0.622**	**0.733**

*NA: some cell numbers too few for kappa calculation.

Table 3 Baseline imaging characteristics in 357 DIPGs

Imaging Feature	N	% Cases*	Note
Tumor Extension			
No extension beyond pons	15	4.2	
Cerebellum	85	23.8	
Midbrain	245	68.6	
Thalami	25	7.0	
Medulla	260	72.8	
Internal capsule	24	6.7	
Brachium pontis	284	79.6	
Extension beyond pons and BP	319	89.4	
% pons involved			
1–33%	1	0.3	
34–66%	21	5.9	
67–100%	335	93.8	
<50%	3	0.8	
>50%	354	99.2	
Tumor Morphology			
Margin (well-defined)	15	4.2	
Eccentric	50	14.0	
Exophytic	229	64.1	
Heterogeneity (marked)	54	15.1	
Atypical features but likely DIPG	92	25.8	
Tumor Signal			
T1 hypointense/T2 hyperintense	336	95.7	351 with both T1 and T2 sequences
T2 hypointensity (any)	189	53.2	2 missing T2 sequence
Non-necrotic T2 hyperintensity (any)	128	36.1	2 missing T2 sequence
Stripes visible	251	70.5	1 incomplete data
Enhancement			
Enhancement (any)	239	68.9	of 347 that had contrast
Homogeneous	2	0.8	of 239 that had enhancement
Ring enhancement	122	51.5	of 239 that had enhancement
Patchy enhancement	162	67.4	of 239 that had enhancement
Patchy and ring enhancement	46	19.2	of 239 that had enhancement
Diffusion/Hemorrhage/Necrosis			
Diffusion restriction (any)	184	63.2	of 291 with diffusion sequence
Hemorrhage (any)	102	28.6	
Hemorrhage (> minimal)	40	11.2	
Hemorrhage (any, GRE/SWI)	73	50.0	of 146 with SWI or GRE sequence
Hemorrhage (>minimal.,GRE/SWI)	31	21.2	of 146 with SWI or GRE sequence
Necrosis (any)	156	43.6	
Necrosis + ring enhancement	118	34.0	of 347 that had contrast
Necrosis with no ring enhancement	37	10.7	of 347 that had contrast
Spectroscopy			
NAA/Cr (decreased)	66	75.0	of 88 with spectroscopy
Cho/Cr (increased)	74	84.1	of 88 with spectroscopy
Cho/NAA (increased)	75	85.2	of 88 with spectroscopy
ml/Cr (increased)	34	41.0	of 83 with assessable ml
Lactate present	56	64.4	of 87 with assessable lactate

Table 3 Continued

Imaging Feature	N	% Cases*	Note
Other Features			
Hydrocephalus	79	22.1	
Subependymal signal	78	21.8	*see note
Distant disease	11	3.1	of 357 cases
Distant disease (spine available)	9	6.8	of 133 with spine imaging

* 26 subjects with no hydrocephalus had subependymal signal, 52 subjects with hydrocephalus had subependymal signal.

small. Selected imaging features were correlated with H3 or WT mutation status (those that were correlated with OS, as well as those potentially related based upon prior published data).[6] No imaging feature correlated with histone status (H3 vs WT or H3.3 vs H3.1; Table 6). The presence of "T2 stripes" was more prevalent in H3 tumors than WT tumors (OR 4.98, $P = 0.03$), and was seen more commonly in H3.1 tumors (90.9%) than H3.3 tumors (58.6%) (not statistically significant). Necrosis and enhancement were also more prevalent in H3.1 versus H3.3 tumors without attaining statistical significance (Table 6).

Discussion

DIPG Definition

We have described the imaging spectrum of DIPGs in a large number of subjects in a multi-institutional registry (IDIPGR), defined specific baseline imaging features and diagnostic criteria, assessed interobserver agreement related to the imaging features, and validated the utility of the imaging descriptors by correlating them with OS. In addition, we have preliminarily assessed the relationship of imaging features in these tumors to histone mutation status. Defining imaging criteria for DIPG and standardizing and validating a defined set of imaging features is an important component of the imaging core of the IDIPGR. These assessments can be used by registry-approved research in the future, and will provide the basis for further studies.[15]

The definition of DIPG is based on both clinical and radiologic features. The concept of "diffuse midline glioma" encompassing diffuse glial origin tumors of the spinal cord, brainstem, thalami, and other midline locations (associated with the H3K27M histone mutation) has been adopted by the WHO and incorporates most of those tumors previously identified as DIPG.[7] DIPG as a general descriptor remains a highly useful clinical-radiologic classification based upon the common clinical presentation, age demographics, imaging appearance, and extensive prior literature related to DIPG, and could include both tumors with H3K27M mutation and WT tumors.

On imaging, DIPGs have previously been described as intrinsic, infiltrative diffuse pontine tumors, typically with brainstem expansion and involvement of 50% or greater of the pons.[2] In this study we did include a small number of subjects (3/357, 0.8%), which involved <50% of the pons (classified as likely DIPG). Each had an imaging appearance that was otherwise compatible with DIPG and on follow-up progressed in a manner that was typical for these tumors.

MR Imaging Characteristics

There have been few large studies focused on evaluating imaging characteristics of DIPG at presentation.[11,16,20,25–27] Although limited imaging features from a portion of this cohort have been incorporated in 2 prior publications in association with SIOPE (one attempting to validate a DIPG prediction model[17] and another looking at predictors of long-term [>2 y] survival),[18] the current study comprises the largest single registry cohort assessing imaging features and survival yet reported.

The imaging features of DIPG in this study are generally similar to those described previously, with some notable differences.

Extrapontine extension (90%), thalamic/internal capsule extension (7%), and enhancement (70%) prevalence are similar to that previously described.[6,11,12,16,20,25–27] Peripheral, ring-like enhancement was seen in 52% of those with enhancement (35% overall) on the lower end of prior reports (overall 38–50%),[6,11,16] which may be due to more stringent criteria used in the current study.

Tumor necrosis has been evaluated previously but has been variably defined, limiting comparisons. Prior studies have referred to presumably necrotic areas as "cyst or necrosis,"[12] "cystic necrosis,"[26] "cyst,"[28,29] or "necrosis"[16,30,31] generally without specific criteria. As detailed in the Supplementary Material (Supplementary 1), we defined necrosis as areas of well-defined, non-enhancing, typically fluid-like signal within the tumor. Because some of the exams did not include post-contrast sequences, peripheral rim-like enhancement was not an absolute criterion for necrosis in this study. As defined, necrotic regions were seen in 44% of tumors (45% of those with contrast administration). Prior literature reports cystic change and/or necrosis in between 20% and 53% of cases, generally similar to the current study. Most regions of necrosis identified in this study (75%) exhibited peripheral, rim-like enhancement when contrast was administered.

Hemorrhage has more rarely been reported in DIPG and performance of SWI or GRE sequences increases sensitivity. Hemorrhage was present in 29% of cases at baseline

Table 4 Univariable analysis of imaging features and overall survival (significant findings)

Univariate	HR	*P*
Clinical		
Age (continuous)	***1.00***	***0.033***
Age		***0.001***
Symptom duration		***0.018***
Chemotherapy	***0.46***	***<0.001***
Midbrain extension	***1.36***	***0.008***
Extension Beyond Pons and BP	***1.64***	***0.002***
Extension Beyond Pons	***2.15***	***0.001***
APTumor dimension	***1.02***	***0.023***
TransTumor dimension	***1.01***	***0.031***
AP XTransTumor dimension	***1.00***	***0.029***
CCTumor dimension	***1.01***	***0.009***
APTumor / AP pons ratio	***2.29***	***0.005***
AP XTRTumor > AP XTR Pons	***1.30***	***0.012***
Enhancement (any)	***1.36***	***0.010***
Ring enhancement vs non-enhancing	***1.45***	***0.007***
Patchy enhancement vs non-enhancing	***1.44***	***0.005***
Patchy and ring enhancement vs non-enhancing	***1.93***	***0.001***
Diffusion restriction (any)	***1.46***	***0.003***
Hemorrhage (any)	1.22	0.098
Hemorrhage (GRE/SWI)	***1.43***	***0.028***
Necrosis (any)	***1.47***	***0.0006***
Necrosis + Ring Enhancement	***1.40***	***0.005***
Necrosis with no Ring Enhancement	***1.48***	***0.034***
Distant Disease	***2.95***	***0.0005***
Distant Disease (spine available)	***2.64***	***0.0031***

Table 5 Multivariable analysis of clinical and imaging features and OS

Variable	HR	*P*
Age		**0.0187**
<3	**0.76**	
3–10	**1.00**	
10+	**0.66**	
Symptom duration		0.1164
<6 weeks	1.00	
6–12 weeks	0.78	
12–24 weeks	0.76	
>24 weeks	0.60	
Chemo	**0.45**	**<0.0001**
Extension beyond Pons or BP	1.10	0.9247
APTumor dimension	0.99	0.3246
TransTumor dimension	1.00	0.8672
CCTumor dimension	1.01	0.1996
APTumor / AP pons ratio	2.26	0.0631
Beyond Pons	1.33	0.7807
Enhancement (any)	1.21	0.2167
Heterogeneity (marked)	0.94	0.7601
Necrosis	1.21	0.1932
Distant Disease	**2.97**	**0.0021**

*Diffusion status removed for missing >10%, AP x Trans and AP x CC for high correlation with AP, midbrain extension since it is included in the definition of extension beyond Pons or BP, extension beyond pons and brachium pontis due to correlation with extension beyond pons, enhancement subtypes due to correlation with enhancement, and hemorrhage with SWI or GRE sequences due to missing >10%).

(50% when evaluating only subjects with GRE or SWI images), similar to prior studies.[12,16,29,30,32]

Localized areas of relative diffusion restriction were identified visually in most tumors (63%). Due to widely differing techniques and available maps, we were unable to perform quantitative assessments. Given the known correlation of lower baseline apparent diffusion coefficient (ADC) and shortened survival in DIPG,[25,33–35] we believed that a visual assessment of diffusion restriction might be useful to describe for future research use and incorporation into the IDIPGR database (Supplementary 1). Similar to other studies, a majority of tumors demonstrated elevated choline, decreased *N*-acetylaspartate (NAA), and visible lactate peaks on spectroscopy.[28,36,37]

The presence of distant disease at diagnosis has been infrequently studied in DIPG, and most DIPG patients (as in this cohort) do not have spine imaging at baseline. Overall, 11/357 (3.1%) subjects had distant disease at diagnosis in our cohort (6.8%; 9/133 when assessing only those with spine imaging at baseline). Prior literature regarding baseline prevalence of distant disease is limited. Between 1% and 19% prevalence rate of distant baseline disease has been described,[12,16,31,38–40] with larger prevalence in those with spinal imaging at baseline.[38] We identified a similar prevalence of distant disease at diagnosis as the SIOPE cohort[16] (1.3%, 2.2% in our cohort) and spinal disease (1.9%; 1.7% in our cohort). The assessment of whether non-contiguous parenchymal tumor is metastatic or multifocal and whether there are biologic and survival differences require further study.

It is important to note that all tumors classified as "likely DIPG with unusual features" were indeed considered DIPG and entered into the registry as such. As noted above, hemorrhage, necrosis, and visible diffusion restriction are common in DIPG, and these features alone should not necessarily indicate an alternative diagnosis.

Interobserver Agreement

While the mean concordance between reviewers was good, there was significant variation in agreement depending upon the specific feature assessed. Given these findings, the IDIPGR imaging database will continue to

Table 6 Imaging features and histone mutation status

Imaging—Genomic Analysis	*Genomic Classification*								*Statistical Comparison*			
	H3		*H3.1*		*H3.3*		*WT*		*H3 vs WT*		*H3.3 vs H3.1*	
Imaging Feature	(*N* = 47)	%	(*N* = 11)	%	(*N* = 29)	%	(*N* = 10)	%	OR	*P*	OR	*P*
Extrapontine extension	43	91.5	11	100	25	86.2	9	90	1.22	0.82	0.31	0.31
AP tumor dimension (mean)	35.3		38.4		34.8		33.7		1.03	0.55	0.94	0.21
AP Tumor/AP Pons (mean)	0.988		0.998		0.992		1.045		0.12	0.29	0.75	0.90
CC tumor (mean)	42.3		46.5		41.1		39.0		1.03	0.37	0.95	0.15
Eccentric	14	29.8	2	18.2	9	31.0	1	10	3.82	0.22	2.03	0.42
Non-necrotic T2 hyperintensity	17	36.2	6	54.5	7	24.1	3	30	1.45	0.62	0.32	0.12
T2 hypointensity	28	59.6	7	63.6	16	55.2	6	60	0.98	0.98	0.63	0.70
Stripes present	32	68.1	10	90.9	17	58.6	3	30	**4.98**	**0.03**	0.14	0.08
Enhancement	38	80.9	10	90.9	22	75.9	10	100	0.29	0.19	0.31	0.31
Peripheral ring like enhancement	22	46.8	6	54.5	14	48.3	7	70	0.59	0.49	1.17	0.84
Diffusion restriction present*	27	60.0	6	54.5	18	64.3	7	70	0.64	0.56	1.50	0.58
Hemorrhage present	21	44.7	5	45.5	13	44.8	4	40	0.79	1.21	0.97	0.98
Necrosis present	27	57.4	8	72.7	17	58.6	7	70	0.58	0.47	0.53	0.41

*Two H3 had no diffusion imaging and one H3.3 had no diffusion imaging.

incorporate reviews by 2 neuroradiologists with disagreements in classification adjudicated by consensus opinion.

Correlation of Imaging Features with Overall Survival

Various features of DIPG have previously been correlated with survival in DIPG[6,11,18,25,26,32]; however, not all studies have found significant associations.[12,30] These differences are likely related to number of cases evaluated, imaging criteria and assessment methods, as well as the difficulty in identifying survival predictors in a tumor that has a very short OS. In the present study, extension of tumor beyond the pons, larger tumor size at diagnosis (especially related to larger AP tumor size relative to AP pons size), enhancement, necrosis, visualized regions of diffusion restriction, and distant disease at diagnosis were associated with shorter OS on univariable analysis (with distant disease remaining significant in multivariable analysis).

Extrapontine extension has been previously evaluated by a few investigators with inconsistent definitions[11,12,30,31,41] and has not previously correlated with shorter survival when assessed.[31,41] Hoffman et al, however, using data from both IDIPGR and SIOPE,[18] found that extrapontine extension was found less frequently in long-term survivors ($P = 0.04$). Both extension of tumor outside of the pons proper or outside the confines of the pons and brachium pontis correlated with shorter OS in our cohort, which may be related to the larger sample size, inclusion of smaller tumors, or more stringent definitions.

Baseline tumor size has been rarely assessed with regard to OS in patients with DIPG. Ahmed et al[30] assessing 25 subjects found no correlation of baseline tumor size with OS. Poussaint et al[26] assessed tumor volumes and found that larger tumor volume pre-radiotherapy correlated with a longer progression-free survival (PFS) but did not report a relationship to OS. Hoffman et al,[18] using data from both IDIPGR and SIOPE, found that long-term (>2 y) survivors had a smaller CC tumor dimension, although there were no significant differences in AP or TR measurement between groups. Larger AP tumor/AP pons measurement ratios (>1) generally occur when the tumor extends laterally or asymmetrically into the brachium pontis and cerebellum, indicating a potentially more advanced stage of tumor extension at baseline (Supplementary 1). Very recently, a study describing decreased survival in DIPG patients with increasing middle cerebellar extension has been published.[42] AP tumor/AP pons ratio may be an important prognostic feature and should be assessed in future studies. Steffen-Smith et al[43] assessed baseline 1D (transverse) and 2D pons dimensions with OS with shorter survival when 2D pons measurements were above the median. This suggests that larger tumors at baseline have worse prognosis. We used the same method[43] but found no statistically significant relationship of 1D or 2D pons size with OS (using Cox proportional hazards regression) or comparing 2D larger than median (1680 mm^2) using Kaplan–Meier analysis (data not shown). Discrepancies could potentially relate to numbers of subjects, different measurement methods, and different survival endpoints.

Enhancement has generally been found to correlate with shorter survival, although this is not universal.[12,28,30,31] Similar to our analysis, most studies have reported shorter OS in those patients with enhancement.[6,11,25,26] Ring enhancement has been noted specifically to be associated with shorter survival by Jansen et al[11] in the SIOPE cohort and incorporated into a survival prediction model.

As stated above, necrosis has been variably defined in prior studies limiting comparisons between investigations. In our study the presence of necrosis was significantly associated with shorter OS on univariable analysis. Hoffman

et al[18] (using combined data from the IDIPGR and SIOPE) found necrosis in a significantly higher proportion of short-term survivors (42%) than long-term survivors (26%). Other investigators describing necrosis in DIPG have either not assessed its relationship to survival[26,29] or found it not significant.[12,28,30,31]

Quantitative assessment of diffusion characteristics of DIPG has been reported, with most reporting some relationship to survival. We found that those tumors with visibly restricted diffusion had shorter OS on univariable analysis. While techniques utilized are varied (region-of-interest, histogram analysis), several authors have reported worse survival (OS and PFS) with lower intratumoral baseline ADC values,[25,33–35,44] consistent with our visual assessment observations.

Careful quantitative studies have shown variable relationships of baseline perfusion imaging with survival.[26,36,45] Detailed quantitative spectroscopy studies have suggested that those tumors with higher choline/NAA ratios[28,36,37] and lactate visualization[28] have shorter survival. Perfusion imaging and spectroscopy could only be evaluated in a subjective fashion in a small number of subjects in this study, and no statistically significant relationship between perfusion status or MR spectroscopy findings and survival was noted. This is not surprising considering the small numbers, non-quantitative assessment, and variable techniques used in the submitted registry imaging data.

Prognostic implications of distant disease at diagnosis in DIPG have been rarely assessed. This study confirms that the presence of distant disease at diagnosis, while infrequent, is a strong predictor of poor OS. A full understanding of the prevalence of distant disease in DIPG is limited by the lack of routine performance of baseline spine imaging in this group.[38,39] While spinal dissemination is rare, consideration should be given to performing spinal imaging at baseline in these patients. Most prior studies have focused on disseminated disease during treatment and relapse,[38–40] with presence of disseminated disease (regardless of local disease status) typically associated with poor prognosis.[38]

Correlation with Histone Status

Very few studies have evaluated imaging in DIPG and histone mutation status. Our study is the first using a large number of registry-defined imaging features to assess differences in imaging appearance between H3 mutated and WT, as well as between H3.3 and H3.1 mutated DIPGs. Although our numbers are small, we did not find a statistically significant relationship between any registry imaging feature and histone status (H3 vs WT or H3.3 vs H3.1). Castel et al[6] found a higher prevalence of necrosis, edema (evidenced by infiltrative T2 signal within the pons, so-called T2-stripes), ring enhancement, and more restricted diffusion (by histogram analysis) in H3.1 versus H3.3 tumors. We also found infiltrative T2 signal (T2-stripes) more prevalent in H3.1 tumors in agreement with Castel et al; however, we did not find any other statistically significant difference between these 2 groups. The trends in our data (more common enhancement and necrosis in H3.1 tumors) are generally consistent with those of Castel et al, with the smaller number of subjects with known histone status in our population a possible explanation. Aboian et al[8] evaluated 33 patients with diffuse midline gliomas (only 14 of pontine origin) and found diverse imaging appearances without distinguishing features between histone H3 and WT diffuse gliomas. The lack of strong correlation with visually identified imaging features and histone mutation status is not surprising, given the poor correlation between histopathology (more strongly predictive of imaging appearance) and histone mutation status.[18] Inherent limitations in visual analysis of imaging studies point out the need for more advanced data-driven approaches, including machine learning, in this patient population.

Surprisingly, we found no correlation between histone status and OS. Previous reports have generally shown a shorter OS in patients with H3.3 mutation versus WT or H3.1,[6] suggesting that H3.3 mutated tumors are more aggressive. Hoffman et al,[18] evaluating 181 subjects in which genomic data were available (combined data from the IDIPGR and SIOPE), documented fewer long-term survivors in those with H3.3 versus H3.1 mutations. They, however, also found no difference in the prevalence of short-term survivors between H3 and WT tumors. The reasons for the lack of correlation between survival and histone status in our study are uncertain but may relate to smaller numbers of subjects evaluated and the use of different techniques than other studies assessing this relationship. There does seem to be a discrepancy between imaging features related to survival and those related to histone status[6] that has not been fully explained or investigated. In our study the presence of enhancement, necrosis, and diffusion restriction are features related to shorter OS. In the study by Castel et al (and supported by trends in our data), these are features that are more prevalent in H3.1 mutated tumors (compared with H3.3 tumors), which exhibit longer OS in most studies that have assessed this feature. Reasons for this discrepancy are unclear, but may be related to an imaging and histopathology independent association of the H3.3 mutation with survival. Although the primary objective of this study was to correlate DIPG imaging features with OS, multivariable analysis found that the use of systemic chemotherapy led to improved OS, as previously reported by Hoffman et al in a combined report from the IDIPGR and SIOPE registries[17] and by others.[46–48] However, the inherent limitations of registry data including enrollment, reporting, and survival bias lead us to interpret this finding with caution. The general consensus remains that systemic therapy provides little survival benefit for patient with DIPG.[48,49] Limitations to this study are discussed in the Supplementary Material (Supplementary 4).

Conclusions

Baseline imaging features were assessed in 357 subjects in the IDIPGR using standardized imaging features which will serve as a resource for ongoing and future collaborative research projects. Nearly 10% of studies submitted to the registry with a local diagnosis of DIPG were categorized as non-DIPG by study reviewers highlighting the need for imaging confirmation by central review for prospective trials.

Multiple imaging features correlate with OS on univariable analysis, helping validate the utility of the imaging classification scheme. Distant disease at diagnosis portends a poor prognosis. There was no statistically significant correlation of imaging features with histone mutation status, although numbers are small and evaluation exploratory. Further in-depth research in genomic-radiologic classifications is needed, in part using advanced imaging techniques such as textural analysis and machine learning to probe for additional correlations.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

diffuse midline glioma | DIPG | histone mutation | international DIPG registry | MRI

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Please see: https://dipgregistry.org/about/supporters/, and Supplementary 5.

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