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The Incidence of Brainstem Primitive Neuroectodermal Tumors of Childhood Based on SEER Data

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Abstract

Purpose—Incidence of BS primitive neuroectodermal tumors (BS-PNET) in children is not reported to date. Our main objectives were to estimate the incidence and report the outcome of BS-PNET in children.

Methods—Data was collected using the Surveillance Epidemiology and End Results cancer registry.

Results—From 1973 till 2013, we identified 83 pediatric patients (aged 0–21 years). Patients were divided into 2 age groups (0–3 years and 4–21 years). Median overall survival was 53 months. Patients in the older age group had a significant survival advantage ($P < 0.001$), as did those who received 3 modalities of therapy (surgery, chemotherapy, and radiation therapy) ($P < 0.001$) and patients with gross or subtotal tumor resection ($P < 0.001$).

Conclusions—This study presents the first estimate of incidence and the largest cohort of pediatric BS-PNETs to date. A high index of suspicion of BS-PNET in similar cases is crucial for diagnosis, treatment, and outcome.

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Contributors' Statement:

Dr. Qaddoumi conceived and designed the study.

Dr. Alfaar acquired and analyzed all of the data.

Drs. Qaddoumi, Alfaar, Chamdine, and Elhawary interpreted the data.

Drs. Chamdine and Elhawary drafted the initial manuscript and approved the final manuscript as submitted.

Drs. Qaddoumi and Alfaar critically revised the manuscript and approved the final manuscript as submitted.

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Keywords

embryonal tumor; brainstem tumor; biopsy; outcome

Introduction

Tumors of the brainstem (BS) account for 10% of all pediatric brain tumors. High-grade gliomas (most commonly, diffuse intrinsic pontine gliomas) account for 85% of pediatric brain tumors and have dismal outcomes, with less than 10% of children surviving 3 years beyond diagnosis, regardless of the treatment modality administered [1]. Low-grade gliomas constitute 15% to 20% of BS tumors. They are usually focal with a variable enhancement pattern. Low-grade gliomas are treated with surgical resection, radiation therapy, and chemotherapy and usually have a more favorable outcome [2]. Since the report of Albright in 1993 [3], biopsy of BS tumors has been reserved for patients with focal tumors or tumors with atypical features on magnetic resonance imaging (MRI) [4]. The decision to biopsy has been controversial because no consensus has been reached on the definition of “atypical features” [5].

Primitive neuroectodermal tumors (PNETs) are a group of embryonal tumors of the central nervous system (CNS) that occur predominantly in children and adolescents. PNETs were first recognized in 1973 [6], but they were not officially included in the World Health Organization classification system until 1993 [7]. These tumors are uncommon and represent only about 1% to 3% of all pediatric CNS tumors [8, 9]. Histologically, they are composed of a diverse group of poorly or undifferentiated neuroepithelial cells [6, 10]. Picard et al. (2012) identified 3 molecular subgroups of supratentorial PNET with differential expression of cell markers LIN28 and OLIG2 [11]. More recently, the analyses of DNA-methylation patterns of histologically diagnosed PNETs led to the discovery of 4 molecular subtypes: CNS neuroblastoma with *FOXR2* activation, CNS Ewing sarcoma family of tumors with *CIC* alteration, CNS high-grade neuroepithelial tumor with *MNI* alteration, and CNS high-grade neuroepithelial tumor with *BCOR* alteration [12].

Traditionally, PNETs are most commonly located in the cerebrum but can arise in the supracellar region or spinal cord. Very rarely has PNET been reported in the brainstem [1, 4, 13–18]. Here we aimed to estimate the incidence of brainstem PNET in children by using a large data set. We also calculated the survival rates and analyzed multiple variables, including age, sex, radiation therapy, and extent of surgical resection, in relation to the outcome.

Methods

Data were extracted from the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) registry. SEER is a comprehensive source of cancer incidence and survival data that covers 28% of the United States population. SEER collects data about all persons who receive a cancer diagnosis and reside within a region covered by 18 collaborating registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, Utah, Los Angeles, San Jose–Monterey, Rural

Georgia, Alaska Native, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey). All pediatric patients (aged 0–21 years) with a diagnosis of BS-PNET, listed in the registry during 1973–2013 (with known age at diagnosis, malignant behavior, cases in SEER research database) were included in the study.

To ensure that we included only patients with BS-PNET, we used the following International Classification of Diseases for Oncology, 3rd edition (ICD-O-3)[19] codes: 9473/3 (CNS PNET), 9500/3 (CNS neuroblastoma), 9490/3 (CNS ganglioneuroblastoma), and 9501/3 (medulloepithelioma). Because anaplastic ependymomas and ependymoblastomas share the same ICD-O-3 code (9392/3), we excluded all patients with this code from our study to avoid any bias. We classified the patients into 2 age groups, 0–3 years ($n = 37$) and 4–21 years ($n = 46$), because of the difference in the treatment approaches for these 2 age groups. Demographic data (age, sex, race, state at diagnosis, tumor characteristics (histology and dissemination), and treatment modalities (surgical resection and radiation therapy) were analyzed (Table 1). Special permission was obtained to access chemotherapy data. Overall survival (OS) was defined as the time from diagnosis until death due to any cause. Surgery data were constructed by combining data from 1983–1997 and that from 1998–2013 and unifying the coding system. The patients with unknown status of treatment delivery were assigned to the category “No delivery.” To estimate the incidence of BS-PNET in the general population, we used the SEER Age-Adjusted Rates Sessions using Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, November 2015, Sub (2000–2013) <Katrina/Rita Population Adjustment>. The incidence analysis was performed for the period 2000–2013 to include all registries that were used to collect data for our study population.

Results

Patient Characteristics

We identified 937 children (0–21 years old) with the diagnosis of PNET in the SEER database from 1973–2013, among 16,991 children affected by brain tumors. This accounted for 5.5% of all CNS tumors in children during this period. The estimated incidence from 2000–2013 ($n = 41$ patients) in the general population was 26 cases per 1,000,000. The incidence according to race and sex is shown in Table 2. The study cohort is summarized in a flow chart (Fig. 1). Patient characteristics are listed in Table 1. The total number of children with BS-PNET was 83 (9% of childhood PNET and 3% of childhood BS tumors). The majority (90%, $n = 75$) of the patients were classified as having PNET, followed by 4% ($n = 3$ each) neuroblastoma not otherwise specified (NOS) and medulloepithelioma NOS. The remaining 2% ($n = 2$) patients were classified as having ganglioneuroblastoma. Tissue diagnosis was completed at autopsy in 26 patients (31.3%), all done after 2003. Nearly all patients had a single primary tumor; 1 patient had 2 primaries. Metastatic disease was not reported in the SEER database prior to 2004. In our cohort, 26 patients were included after 2004. Among them, 4 had metastases within the CNS; 1 had extraneural metastatic disease; and disease status was unknown in 4 cases. The mean age at diagnosis was 6 years. The occurrence of BS-PNET was a bit higher in the older age group (45% vs 55%, respectively). The incidence was higher in boys (68%) than in girls (32%), and the predominant race was

white (88%). Only 1 pediatric patient with BS-PNET was reported in the registry before 1982.

Treatment and Outcome

Forty-two (51%) patients received combined chemotherapy, surgical resection, and radiation therapy. Eighteen (22%) had surgical resection and chemotherapy. No information was available about treatment of 5 cases (6%). Most patients in the younger age group underwent surgical resection and received chemotherapy ($n = 16$, 43%), whereas the majority (67%, $n = 31$) of patients in the older age group underwent surgical resection and received chemotherapy and radiation therapy.

Median OS for the entire cohort was 53 months (95% CI, 0–133.66 months) (Table 1). There was no significant difference in survival related to race or sex. Patients in the older group had a significant survival advantage over those in the younger group; 5-year OS was 63% vs. 30%, and 10-year OS was 60% vs 26%, ($P < 0.0005$) (Fig. 2). Patients who received all 3 treatment modalities (surgery, chemotherapy and radiation therapy) fared the best (5-year OS, 65%; 10-year OS, 59%), compared with those who received 2 treatment modalities (OS, 36%) or 1 modality (OS, 26%) (Fig. 2). Regardless of the era of diagnosis, gross-total resection (GTR) and subtotal resection (STR) were superior (5-year OS, 80%) to any surgery that resulted in less than STR or no surgery. Patients who received radiation therapy also had a superior outcome. Table 1 summarizes survival results.

Discussion

BS-PNET is a rare disease, and only a limited number of cases has been reported in the literature [1, 4, 13–16, 18, 20]. Previously, the largest number of cases in a single report was 7 (Table 3.). There is no documentation of the incidence of BS-PNET in childhood. Our study represents the largest sample of children with BS-PNET derived from the SEER database. Here we reported 83 cases of pediatric BS-PNET, which comprised 9.1% of all childhood PNETs in the SEER database. This cohort is most likely to reflect the incidence of BS-PNET cases in the U.S., as the demographics of patients captured by SEER is known to be representative of those in the U.S. [21, 22].

Since Albright et al. published their report on BS tumors in 1993 [3], patients with such tumors have rarely undergone biopsy, and the diagnosis has been made based on radiologic criteria. Most of the patients received a diagnosis of BS gliomas and were treated with focal radiation therapy [23, 24], especially after the failure of multiple combination therapies, including high-dose chemotherapy with stem cell transplantation to improve the dismal prognosis [16]. In addition, biopsy and resection of BS tumors were considered high-risk procedures and thus were performed only in rare cases. These factors, in addition to the poor imaging accuracy prior to the MRI era in the early 1990s and the limited power of histopathology in the earlier years to differentiate tumors, played an essential role in underestimating the incidence of tumors other than gliomas. Only 1 case of BS-PNET was reported before 1982 in the SEER database, and the first case in the literature was reported in 1996 [20]. In our cohort, all of the patients had histopathologic confirmation, either at diagnosis ($n = 57$) or autopsy ($n = 26$). Two cases with diagnosis at autopsy were reported in

the literature [18]. Similar to the reported cases [1, 4, 13–16, 18, 20], SEER cases included PNET as the most common histopathologic diagnosis, followed by medulloepithelioma.

Zagzag et al. concluded that age younger than 3 years at diagnosis was more suggestive of BS-PNET [1]. The mean age of our cohort was 3 years, which was similar to that in the literature (3.7 years). However, slightly larger proportion of our patients were older than 3 years (55.4%, median is 4 years old) as compared to in the literature (median is 3 years old). Metastatic disease is common in patients with PNET at diagnosis [1], and similar findings were noted in patients with BS-PNET [1, 4, 16]. Unfortunately, in our cohort, metastasis status was reported for 26 cases only; 5 (19.2%) patients had metastases at diagnosis. This was comparable to the proportion of cases in the literature with metastases at diagnosis (4 of 16, 25%) [1, 4, 16]. Tumor location and MRI characteristics became an essential part in decision making about possible histopathologic diagnosis and the need for biopsy or resection versus radiologic diagnosis. Focal pontine tumors that are well circumscribed, with low signal on T1, bright signal on T2, and have no enhancement after contrast are more commonly associated with BS-PNET [1, 4, 17]. These neuroradiologic characteristics, though suggestive of BS-PNET, are not exclusive. Because PNETs can have various degrees of vascularity, tumor enhancement can vary greatly from intensely enhancing to nonenhancing [1]. Therefore, the differential diagnosis of BS tumors is common, and the ability to establish an accurate diagnosis is limited without obtaining tissue. Fortunately, as neuroimaging technology has advanced, neurosurgical methods have advanced in parallel, and neurosurgeons are more prone to biopsy BS tumors with special indications.

Most reported BS-PNET cases in the literature were focal with various T1 and T2 characteristics (Table 4). One deficiency of this study is our inability to obtain details about the imaging characteristics of the patients and the difference in imaging modalities according to treatment era.

Treatment of PNETs in children older than 3 years comprises maximum safe surgical resection, radiation therapy to the craniospinal axis with a boost to the original tumor bed, followed by chemotherapy. In children younger than 3 years, craniospinal radiation therapy is avoided to prevent the devastating long-term effects. Most studies have used chemotherapy with or without focal radiation therapy [25–27], and some have treated younger children with high-dose chemotherapy and used radiation therapy only as salvage upon recurrence [16]. This was evident in our cohort, in which patients younger than 3 years and those who did not receive radiation therapy fared worse than older patients and those who received radiation therapy. The SEER database does not include details about radiation therapy (focal vs craniospinal) or chemotherapy. Only 3 of 28 (10.7%) patients in the literature were alive at the time of reporting (Table 3). One patient was 3 years old, and another was 2 years old; both received craniospinal radiation therapy following high-dose chemotherapy. The age of the third patient was not reported. In our study, 38 (45.8%) patients were alive at the time of data collection, and patients older than 3 years showed a significant OS advantage.

Our study is not without limitations. The data are retrospective, and some samples could have been miscoded or misclassified, especially those from the older eras. However, using a

large population-based sample from the SEER database increased the power and minimized ascertainment bias in our data. Chemotherapy is a major component of therapy for PNET across all age groups and is especially vital for patients younger than 3 years, for whom radiation therapy is often delayed and confined to the tumor bed [25, 27, 28]. Considering the moderate sensitivity and high specificity of SEER chemotherapy data and that it does not report the type of chemotherapy, the cause of not receiving chemotherapy, or the treatment course thus it cannot represent the efficacy or effectiveness of chemotherapy without caution. We believe that it is less likely that medulloblastomas were mislabeled as PNETs, because they have long-been recognized, and pathologists are well acquainted with the histologic and radiologic appearance of medulloblastomas. Finally, specifications about surgical procedures and radiation therapy are limited in the SEER database.

Conclusion

BS-PNET might not be as rare of a disease as it is thought to be. BS tumors, especially those with atypical features, should be subjected to histopathologic analysis before treatment is initiated. Although SEER data has numerous limitations, it is obvious that the diagnostic approach, treatment modalities, and consequently outcomes of such patients dictate the need to better study and understand this disease. Discovery of new molecular markers and subclassification of PNETs holds promise for predicting clinical outcome and developing targeted therapies, given that surgical resection can be more challenging in this area of the brain.

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Abbreviations

BS	brainstem: BS
CI	confidence interval
CNS	central nervous system
GTR	gross-total resection
MRI	magnetic resonance imaging
NOS	not otherwise specified
OS	overall survival
PNET	primitive neuroectodermal tumor
SEER	Surveillance Epidemiology and End Results
STR	subtotal resection

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Fig. 1.
Flow chart of the study cohort.

Fig. 2.

Overall survival of the patients compared to other groups and within the study groups. (A) Study group compared to tumors of other brain sites. (B) compared to PNET from other brain regions. (C) Comparing age groups within PNET. (D) Comparing patients according to the year of diagnosis. (E) According to therapeutic modality. (F) According to number of therapeutic modalities used.

Table 1

Patients' characteristics and survival according to different variables.

	Number (%)	Mean (95% CI)	Median (95% CI)	Log Rank p-value
Overall	83	145.8 (113.95–177.66)	53.00 (0.00–133.66)	
Age groups (yrs)				
0–3	37 (44.6)	87.6 (44.66–130.55)	14.0 (9.76–18.25)	<0.0004
4–21	46 (55.4)	188.28 (147.62–228.93)		
Sex, Female: Male ratio = 0.48:1				
Female	27 (32.5)	118 (70.43–165.56)	31	0.608
Male	56 (67.5)	148.67 (110.88–186.46)	82 (5.28–158.73)	
Race				
White	71 (87.7)	145.19 (110.85–179.53)	53 (0–135.52)	0.688
Black	2 (2.5)	25 (8.37–41.63)	13	
Other	8 (9.9)	75.375 (17.33–133.43)	9 (0–40.88)	
Treatment *				
RTh, Surg and CTh	42 (50.6)	187.75 (145–230.49)		0.00004 for all. 0.038 between groups containing > 10 patients (The first two groups)
Surg and CTh	18 (21.7)	84.24 (37.55–130.92)	16 (6.59–25.41)	
RTh and Surg	5 (6)	189.67 (73.91–305.43)		
Surg only	5 (6)	93 (13.59–172.41)	15	
CTh only	4 (4.8)	14.250 (0.79–27.71)	5 (0–15.78)	
RTh only	2 (2.41)	6 (0.12–11.88)	3	
No reported therapy	2 (2.41)	18.00 (0–53.28)	0	
Surgery (degree of resection) **				
GTR	35 (42.17)	215.01 (170.89–259.13)		0.001
STR	10 (12.05)	105.222 (31.21–179.23)	46 (0–13.65)	
Biopsy or excision of tumor	22 (26.5)	115.43 (62.72–168.13)	53 (0–17.43)	
No primary cancer-directed surgery	11 (13.25)	42.64 (3.21–82.06)	11 (7.76–14.24)	
Radiation				
Yes	54(65.06)	166.54 (127.54–205.54)		0.043
No	29 (34.9)	80.44 (43.78–117.1)	16 (12.64–19.36)	
Year of diagnosis ***				
1983–1992	16 (19.3)	91.63 (31.44–151.82)	14 (0–31.64)	0.174
1993–2002	39 (47)	137.92 (100.48–175.36)		
2003–2013	27 (32.5)	62.97 (44.23–81.71)		

Abbreviations: yrs, years; RTh, radiotherapy; Surg, surgery; CTh, chemotherapy

* Treatment information was not available for 5 patients

** One patient incisional or needle biopsy and 4 patients with unknown surgery were removed from survival analysis.

*** One (1.2%) patient was recorded between 1973–1982

Table 2

Incidence rates of BS-PNET in USA between 2000–2013 per 1,000,000 Age-adjusted to US standard population.

Gender	Race	Number	Rate/million (95%CI)
Both	All	41	0.11(0.08–0.15)
Male	All	29	0.16 (0.11–0.23)
Female	All	12	0.07 (0.04–0.14)
Both	White	34	0.13 (0.09–0.18)
	Black	2	0.04 (0–0.14)
	Asian or Pacific Islander	3	0.09 (0.02–0.26)
Male	White	24	0.18 (0.11–0.26)
	Black	1	0.04 (0–0.2)
	Asian or Pacific Islander	2	0.11 (0.01–0.41)
Female	White	10	0.08 (0.04–0.14)
	Black	1	0.04 (0–0.21)
	Asian or Pacific Islander	1	0.06 (0–0.35)

Abbreviations: CI, confidence interval. Patients with unknown race (n= 2) not shown.

Table 3

Summary of reported BS-PNET cases.

Study (Number of patients)	Age (years)	Presentation/symptom duration PTP	Surgical intervention	Histologic diagnosis	Metastatic disease	Treatment	Survival (months)
Suft et al. ⁴ (2)	1.3	CN deficits/hemiparesis 5 d	Bx of metastatic lesion in the spine	PNET	Yes (spine)	Tandem ASCT and RT	NR
	2.3	CN/hemiparesis 3 weeks	Bx	PNET	No	Tandem ASCT and RT	NR
Zagzag et al. ¹ (7)	1	CN/1 m	Bx of metastatic site	PNET with foci of ependymal/ependymoblastic differentiation	Yes	4 patients received CSI with multiagent chemotherapy. Three patients received chemotherapy only (infant protocol CCG 9921)	4
	1.1	CN/1 m	PR		No		10
	1.5	CN, hemiparesis/3 m	PR		No		17
	2.7	CN, hemiparesis/1 m	PR	PNET with foci of ependymal/ependymoblastic differentiation	Yes		3
	4.5	CN, ataxia/1 m	PR		Yes		7
	7.5	CN/6 m	PR		No		8
	8.0	CN, diplopia/1 m	Bx of metastatic site		No		7
	NR	NR	NR	PNET n=4 Medulloepithelioma n=2	At recurrence	NR	NR
Rorke et al. ¹³ (6)							
Molloy et al. ¹⁴ (2)	4.3	Headache, dysarthria, CNP, hemiparesis	Bx at progression	Medulloepithelioma		Focal RT+CHt	20
	3	Irritability, CNP, hemiparesis, dysmetria	Bx at progression	Medulloepithelioma	Not evaluated	Focal RT	23
Lesniak et al. ¹⁵ (1)	NR	NS	GTR	PNET	NS	NS	Alive >10 yrs
Fangusaro et al. ¹⁶ (6)	3	NS	Bx	PNET	M0	As per HS II + CSI	Alive at 32
	4		Bx	PNET	M0	HS II + CSI	Dead
	4.5		Bx	PNET	M3	HS II + CSI	Dead
	3.1		Bx	PNET	M0	HS I	Dead
	2		Bx	PNET	M0	HS II + CSI	Alive at 38
	0.2		STR	PNET	M0	HS I	Dead (NR)

Study (Number of patients)	Age (years)	Presentation/symptom duration PTP	Surgical intervention	Histologic diagnosis	Metastatic disease	Treatment	Survival (months)
Behnke et al. ¹⁹ (4)	14	CNP, hemiparesis, ataxia/1 m	STR	PNET with gangliocytic and chondroid differentiation	NR	None	0.5
	1	CNP, hemiparesis, ataxia/2 m	STR	PNET	NR	None	3
	3	CNP, hemiparesis, ataxia/1 m	STR	PNET	NR	CHt	6
	7	CNP, hemiparesis, ataxia/2 m	STR	PNET	NR	RT and CHt	13
	NR	CNP, ataxia and/or long tract signs	Autopsy	PNET	NR	Focal RT +/- temozolomide	Dead (NR)
Angelini et al. ¹⁸ (2)							
Summary Total number of patients n=30	Mean age 3.76 years (0.2–14)		Bx n=11 GTR/STR n=6 PR n=5 Autopsy n=2 NR n=6	PNET n=26 Medulloblastoma n=4	Metastatic disease n=6/16 (4/6 at diagnosis)		Alive 3/28 (10.7%)

Abbreviations: PTP, prior to presentation; d, days; CN, cranial nerve; Bx, biopsy; m, months; ASCT, autologous stem cell transplantation; HS, Head Start; RT, radiation therapy; PNET, primitive neuroectodermal tumor; NR, not reported; PR, partial resection; CNP, cranial nerve palsy; CHt, chemotherapy.

Table 4

MRI characteristics of BSPNET patients reported in the literature.

		MRI characteristics
Sufit et al. ⁴ (2)	1	<i>Brain</i> : Nonenhancing expansile pontine mass encasing the basilar artery and anterior extension into the supracellar cistern and encasement of the pituitary stalk showing restricted diffusion. <i>Spine</i> : multiple lesions with the largest at the cauda equine at L2 level
	2	Nonenhancing, expansile eccentric pontine mass with extension into the cerebral peduncle
Zagzag et al. ¹ (7)	3	Focal pontine based with extension to medulla and midbrain. Nonenhancing. T1 hypointense, T2 hyperintense
	4	Focal pontine based with extension the left middle cerebellar peduncle. Nonenhancing. T1 hypointense, T2 hyperintense
	5	Focal pontine based with extension to medulla and midbrain. Nonenhancing. T1 hypointense, T2 hyperintense
	6	Focal pontine based with extension the right middle cerebellar peduncle. Nonenhancing. T1 hypointense, T2 NR
	7	Focal originating from left middle cerebellar peduncle extending to the pons. Nonenhancing. T1 hypointense, T2 hyperintense
	8	Focal, enhancement NA. T1 hypointense, T2 hyperintense
	9	Diffuse, pontine based with extension to right middle cerebellar peduncle. Nonenhancing. T1 hypointense, T2 hyperintense
Rorke et al. ¹³ (6)	10–15	Medulla n=2 Interpeduncular cistern n=2 (involving the region of the 3 rd cranial nerves Brainstem (unspecified location): well circumscribed without surrounding edema or enhancement n=2 (medulloepitheliomas)
Molloy et al. ¹⁴ (2)	16–17	Focal, well circumscribed pontine based with minimal heterogeneity. Nonenhancing
Lesniak et al. ¹⁵ (1)	18	#Brainstem, enhancing
Fangusaro et al. ¹⁶ (6)	19–24	#Brainstem Neuroaxis evaluation performed in all cases following surgery (MRI spine + LP)
Behnke et al. ¹⁹ (4)	25	Focal, hypointense pontine based mass with extension to superior cerebellar peduncle. Homogenous contrast enhancement.
	26	Focal, circumscribed, hypointense pontine based mass with extension to superior cerebellar peduncle. No contrast enhancement
	27	Focal, clearly demarcated from surrounding tissue, pontine based mass with extension to superior cerebellar peduncle. No contrast enhancement
	28	Focal pontine based mass with extension to superior cerebellar peduncle. No contrast enhancement.
Angelini et al. ¹⁸ (2)	29–30	Classical DIPG radiologic criteria (tumour involving at least 2/3 of the pons, hyperintense on T2 or Fluid Attenuated Inversion Recovery (FLAIR) sequences, without exophytic component, with or without extension to the adjacent medulla or midbrain and with or without encasement of the basilar artery)

Abbreviations: n, number; #details not provided; DIPG, diffuse intrinsic pontine gliomas