Childs Nerv Syst (2016) 32:269–280
DOI 10.1007/s00381-015-2968-z

ORIGINAL PAPER

Pediatric thalamic tumors in the MRI era: a Canadian perspective

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Received: 28 September 2015 / Accepted: 17 November 2015 / Published online: 23 November 2015

Abstract

Background Thalamic gliomas are rare. The natural history is unpredictable, and the optimal management of these tumors in children is poorly defined. The aim was to identify outcomes, prognostic factors, and response to various modalities of treatment in a relatively large population of pediatric thalamic tumors from many centers within a fairly homogeneous health care system.

Methods We performed a Canadian multicenter retrospective review of pediatric thalamic tumors presenting during the MRI era (1989–2012). Radiology and pathology were reviewed by central independent reviewers. Paraffin shavings for RNA extraction were taken and tested for fusion events involving KIAA1549:BRAF. Tumors were classified as unilateral or bithalamic based on their origin on imaging. Univariate and multivariate analyses on factors influencing survival were performed.

Results Seventy-two thalamic tumors were identified from 11 institutions. Females represented 53 % of the study population, and the mean age at presentation was 8.9 years. Sixty-two tumors were unilateral and 10 bithalamic. Unilateral tumors had a greater propensity to grow inferiorly towards the brainstem. These tumors were predominantly low grade in comparison to bithalamic tumors which were high-grade astrocytomas. The 5-year overall survival was 61±13 % for unithalamic tumors compared to 37±32 % for bithalamic tumors (p=0.097). Multivariate analysis indicated tumor grade as the only significant prognostic factor for unithalamic

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tumors. Six unilateral tumors, all low grade, were BRAF fusion positive.

Conclusion Unilateral and bilateral thalamic tumors behave differently. Surgical resection is an appropriate treatment option in unilateral tumors, most of which are low grade, but outcome is not related to extent of resection (EOR). Bilateral thalamic tumors have a poorer prognosis, but the occasional patient does remarkably well. The efficacy of chemotherapy and radiotherapy has not been clearly demonstrated. Novel therapeutic approaches are required to improve the prognosis for malignant unilateral thalamic tumors and bilateral thalamic tumors.

Keywords Brain tumor · Thalamic tumor · Outcome · Pediatric · Glioma · Surgery · Radiotherapy · Chemotherapy · Thalamus

Introduction

Thalamic gliomas are rare, constituting 1–5 % of pediatric intracranial tumors [1–5]. The natural history is unpredictable, and the optimal management of these tumors in children is poorly defined. Traditionally, thalamic tumors were considered inoperable because of their proximity to critical structures and the risk of major postoperative morbidity [3, 6, 7]. However, with better neuroimaging and intraoperative technology, surgical resection of some thalamic tumors has been achievable with acceptable morbidity.

The goal of this study was to analyze patients with thalamic tumors treated at pediatric neurosurgical centers across Canada over the last 20 years—a time when MRI scans were available. The aim was to identify outcomes, prognostic factors, and response to various treatment modalities in a relatively large population of thalamic tumors from many centers within a fairly homogeneous health care system.

Materials and methods

We performed a retrospective review of pediatric thalamic tumor cases presenting to hospitals across Canada between 1989 and 2012. Patients less than 18 years with MRI diagnosis of thalamic tumor were included. Patients were excluded if it was determined in a central neuroradiological review that the tumor arose from an adjacent structure and involved the thalamus secondarily.

Clinical data on demographics, signs and symptoms, imaging characteristics, patterns of tumor extension, histology, treatments received, and follow-up were collected. Neuroimaging was reviewed independently by a single pediatric neuroradiologist (KP). Tumors were classified into two groups, unilateral and bithalamic, based on MRI. Unilateral tumors were those arising predominantly from one side of the thalamus (Fig. 1a), even if they involved the opposite thalamus to a lesser extent. Bilateral tumors were those which seemed to arise bilaterally in both thalami (Fig.1c). Data analysis was done separately for the two groups to identify prognostic factors for each.

Extent of resection was divided into gross total resection (100 % removal), near-total removal (95–99 % removal), subtotal resection (75–95 % removal) and partial resection (<75 % removal). This information was based on post-surgical imaging, supplemented by the information in the operative notes. Sectional 2D measurements (not 3D volumetry) were used by the reference neuroradiologist to determine the extent of resection.

Pathology specimens, if available, were sent for review and diagnosis by a single neuropathologist (CH). Only these centrally reviewed specimens were included in the statistical analysis. Where possible, paraffin shavings for RNA extraction were taken and tested for fusion events involving KIAA1549:BRAF. Fusions were tested using NanoString nCounter technology (Seattle, Washington). A custom CodeSet for the direct and multiplexed interrogation of the most common fusion variants was designed. Control genes for RNA quality were also included. Blocks were identified only by a number assigned by the sending center, and the tissue was reviewed blindly by the reference neuropathologist (CH). Tumors were designated according to the WHO 2007 Classification of Tumors of the CNS.

Statistical analysis was done using the SPSS 22 statistical package (SPPS Inc.). Progression free survival (PFS) and overall survival (OS) were determined using Kaplan-Meier

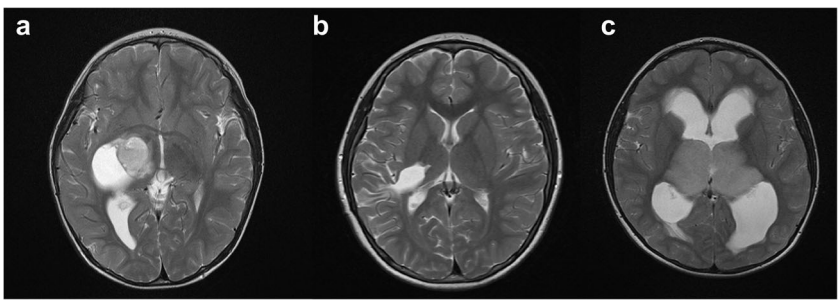

Fig. 1 MRI T2W of **a** unilateral thalamic tumor pre-resection; **b** unilateral thalamic tumor post gross total resection; **c** bilateral thalamic tumor

Table 1 Breakdown of pathology samples reviewed centrally

Pathology samples centrally reviewed (n=47)	Number of cases
Congruent with home institution diagnosis	23
Central review diagnosed tumor (non-diagnostic at home institution)	7
Discrepancies between central pathology and original diagnosis	17
Tumor grade changed from low to high	4
Tumor grade changed from high to low	3
Tumor grade was consistent but different pathology	10

survival plots. Progression was defined as continued growth or relapse of tumors. Differences in OS between predictive groups, such as tumor grade, symptom duration, and extent of resection (EOR), were calculated using univariate analysis through Kaplan-Meier plots. A Cox model was used to evaluate the significance of the predictive factors, and results were considered statistically significant at a probability value (p) of less than 0.05. A multivariate analysis was performed using a binary linear regression model to delineate the significant predictive factors influencing survival indicated by univariate analysis.

Results

Demographics

Between 1989 and 2012, 72 patients with thalamic tumors were identified from 11 pediatric institutions across Canada, who satisfied the inclusion criteria for the study. Another 36 patients had been submitted as thalamic tumors but were excluded on central radiological review. Females represented 53 % (38), and the mean age was 8.9 years (range 0.4–17.9 years). Forty-seven pathology samples were reviewed centrally (Table 1). Of the remaining 25 thalamic tumor cases that did not have samples available for review, 15 had a diagnosis at their home institution, and 10 had no tissue available for diagnosis.

Table 2 Clinical presentations of unilateral and bilateral thalamic tumors

Clinical features	Unilateral (n=62)		Bilateral (n=10)	
	Number	%	Number	%
Raised ICP	43	69	7	70
Motor deficits	20	32	3	30
Sensory deficits	6	10	0	0
Movement disorder	18	29	5	50
Visual problems	10	16	2	20
Seizures	2	3	0	0
Gait ataxia	12	19	4	40
Behavioral changes	10	16	3	30
Dysphasia	2	3	1	10

Unilateral thalamic tumors

Sixty-two tumors (86 %) were unilateral, of which 30 (48 %) were in males. Mean age at diagnosis was 9.2 years and mean duration of symptoms 8.7 months. Sixty-nine percent presented with increased intracranial pressure (ICP). Less common symptoms included motor deficits, movement disorders, and gait ataxia (Table 2).

Radiology

On MRI (Table 3), 68 % were heterogeneous on T2W and 61 % exhibited contrast enhancement post gadolinium injection. In 19 (31 %), the tumor was cystic, of which 8 were pilocytic astrocytoma, 5 were high grade tumors, and 1 was an ependymoma (Table 4). Ventriculomegaly was present in 47 cases. Thirty-eight (61 %) extended inferiorly into the hypothalamus, peduncle, pineal, or midbrain. Seven (11 %) had superior extension into the lateral ventricles, 8 (13 %) laterally into the basal ganglia and hemisphere, 3 (5 %) medially into the third ventricle and 2 (3 %) had multiple involvement. Four tumors (6 %) were localized to the thalamus. Three cases had NF1. Tumor extension patterns are demonstrated in Fig. 2.

Pathology

In 42 (68 %) of the unilateral thalamic tumors, specimens were available for review by the study neuropathologist. Low-grade gliomas accounted for 28 (65 %) cases, including pilocytic astrocytoma, pilomyxoid astrocytoma, diffuse astrocytoma, or non-specific low-grade astrocytoma (3 cases). High grade tumors (14 cases (35 %)) included anaplastic

Table 3 Radiologic characteristics on MRI T2 weighted imaging for unilateral and bilateral thalamic tumors

	Unilateral (n=62)		Bilateral (n=10)	
	Number	%	Number	%
Homogeneous enhancement	20	32	4	40
Heterogeneous enhancement	42	68	6	60
Calcification	13	21	2	20
Cysts	19	31	0	0
Perilesional edema	19	31	2	20
Contrast enhancement	38	61	2	20
Ventriculomegaly	47	76	10	100
Bleed within tumor	2	3	0	0

Table 4 MRI T2 weighted imaging characteristics of unilateral thalamic tumors separated by tumor type

	Pilocytic astrocytoma (n=12)	Other benign* tumor (n=13)	High grade (n=17)†	No pathology (n=20)
Homogeneous	1	6	4	9
Heterogeneous	11	7	13	11
Cysts	8	2	4	5
Calcification	3	1	3	6
Contrast enhancement	9	8	12	9
Perilesional edema	2	4	8	5
Hydrocephalus	9	11	13	14
Bleed within tumor	0	1	1	0

*Other benign tumor types include: diffuse astrocytoma (n=4), pilomyxoid astrocytoma (n=2), ganglioglioma (n=2), central neurocytoma (n=2), ependymoma (n=2), and increased cellularity (n=1).

†Anaplastic astrocytoma (n=4), anaplastic oligodendroglioma (n=1), anaplastic ependymoma (n=4), and glioblastoma (n=8)

astrocytoma (9), glioblastoma (3), and one case each of anaplastic ganglioglioma and germinoma.

Surgery

Eleven patients were managed initially with observation without tissue sampling. Twenty-three had biopsies: stereotactically (7), ventriculoscopically (8), open (3), ultrasound guided (4), and ventriculoscopic plus ultrasound guided in 1. Two required repeat biopsy because of inadequate/inconclusive pathological diagnosis. Both inconclusive biopsies were stereotactic needle biopsies, and both subsequent biopsies were via open access. Tumor resection was performed in 39 patients during the study follow-up period. Out of the 39 patients, 28 had surgical resection for initial tumor management. Resections were performed in 10 patients after initial biopsy only (5 immediately after biopsy; 5 after tumor progression). One patient had resection after initial observational management. Five patients, who initially had surgical resection, received additional excision surgeries for progressive disease. The remaining 23 patients were followed with no additional surgery after their initial surgical tumor resection (Table 5).

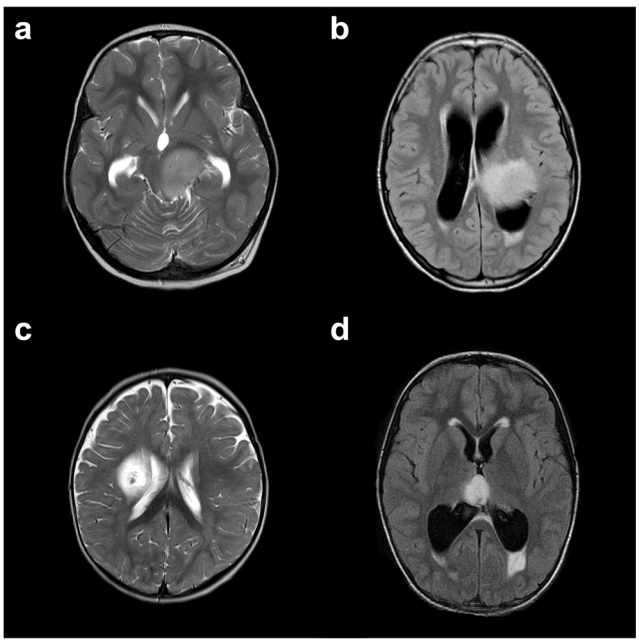

Fig. 2 MRI of unilateral tumors that extend: **a** inferiorly; **b** superiorly; **c** laterally; **d** medially

Table 5 Summary of surgical treatment of unilateral and bilateral thalamic tumors

Initial treatment		Number of cases	Subsequent treatments		
			Biopsy	Resection	No additional treatment
Unilateral	Observation	11	2	1	8
	Biopsy	23	2	10	11
	Resection	28	0	5	23
Bilateral	Observation	1	0	0	1
	Biopsy	9	1	0	8
	Resection	0	0	0	0

The surgical approaches used for resection are summarized in Table 6. Gross total resection (100 % removal) was obtained in 12 (Fig. 1b), near-total removal (95–99 % removal) in 9, subtotal resection (75–95 % removal) in 8 and partial resection (<75 % removal) in 10 tumors. The influence of tumor extension on degree of resection is demonstrated in Table 7.

Of the unilateral thalamic tumor patients who had a surgical resection, 43 % had no neurological deficits, 14 (38 %) had motor and 5 (14 %) visual deficits post-resection. Seven (19 %) had permanent neurological deficits after surgery (5 motor, 2 visual). None of the patients who underwent biopsy developed a post-procedure complication.

Hydrocephalus was present in 38 (53 %) cases of unilateral thalamic tumors. Ventriculoperitoneal (VP) shunts were inserted in 14, and endoscopic third ventriculostomy (ETV)

Table 6 Surgical approaches for resection in unilateral thalamic tumors

Approach	Number (n=39)
Transcallosal frontal interhemispheric	10
Transcortical frontal	11
Transcortical temporal	7
Transcortical parietal/occipital	5
Suboccipital transtentorial	3
Other	3

Table 7 Extent of resection based on unilateral tumor extension

Extension	≥95 % Resection (n=21)	<95 % Resection (n=41)
Inferior (38)	11	27
Lateral (8)	3	5
Superior (7)	3	4
Medial (3)	1	2
Multiple extension (2)	2	0
No extension (4)	1	3

was performed in 9. Hydrocephalus resolved in the remaining 15 patients after tumor debulking (some had an external ventricular drain in situ while awaiting resective surgery).

Adjuvant treatment

Thirty-three patients received no adjuvant chemotherapy or RT (10 PA, 3 ependymoma, 2 diffuse astrocytoma, 1 anaplastic astrocytoma, 1 glioblastoma, 1 pilomyxoid astrocytoma, 1 central neurocytoma, 1 ganglioglioma, and 13 without pathology). Five (8 %) received only radiation therapy; 2 after surgical resection, 2 post biopsy, and 1 post observation followed by biopsy (Table 8). Nine (14 %) patients received only chemotherapy; after biopsy in 2, after surgical resection in 3 and after initial biopsy with subsequent resection in 4. Both chemotherapy and radiation therapy were used for adjuvant treatment in 15 (24 %) unithalamic tumor cases in this series.

Of the patients who received radiation therapy and where there was also a pathology specimen available (15/20), 13 had high-grade lesions, which suggests that the majority of unilateral tumors that received radiation had high-grade pathologies. Thirteen of the patients who received radiation therapy also had a resection and 3 of these cases had >95 % resected. The median radiation tumor dose given to unilateral thalamic tumor patients was 54.5 (36–60) Gy.

Seven of the nine patients who received adjuvant chemotherapy alone had pathology available and in all cases the lesion was low grade. Chemotherapy regimens used for high-grade, unilateral thalamic tumors (n=12) included the following: temozolamide according to ACNS 0126 (4); Procarbazine Lomustine Vincristine (PCV) (2); temozolamide and lomustine according to ACNS 0423 (2); Vincristine, cyclophosphamide, carboplatin (1); Vincristine (1); Carboplatin (1); and carboplatin, vincristine, cyclophosphamide, cisplatin according to COG 99701 (1). Chemotherapy regimens used for low-grade, unilateral thalamic tumors (n=7) included the following: carboplatin, vincristine according to COG 9952 regimen A (4); lomustine, thioguanine, procarbazine and vincristine according to COG 9952 regimen B (1); ifosfamide, carboplatin, etoposide (1); and vincristine, cyclophosphamide, etoposide, cisplatin according to POG 9233 Regimen A (1). There were 5 patients without centrally reviewed pathology who received the following chemotherapy regimens: Methotrexate, cisplatinum, etoposide, vincristine (1); Metronomic temozolamide (1); ACNS 0423 (1); COG 9952 Regimen A (1); and ACNS 0126 (1).

Outcome

The average length of follow-up for patients with unilateral thalamic tumors was 47.3 months (median 37.4 months; range 0.83 to 235.2 months). The 5-year PFS was 54±14 % and the 5-year OS was 61±13 % (Fig. 3).

Analysis of the factors influencing OS in unilateral thalamic tumors is summarized in Table 9 and shown in Fig. 4. High-grade tumors had a much lower 5-year OS (7±13 %) compared to low-grade tumors (84±17 %) (Fig. 4a). Five-year OS was 80±18 % for patients with near/gross total resections (≥95 % resection) and 52±16 % for patients with less than 95 % tumor removal (no resection, biopsy, subtotal, or partial resection) (Fig. 4b). Survival time was significantly different on univariate log-rank tests between the 2 EOR groups (p= 0.043). Patients with symptoms lasting longer than 3 months before diagnosis had a 5-year OS of 86±15 %, while patients with symptoms lasting less than 3 months before diagnosis had a 5-year OS of 42±17 % (Fig. 4c). Patients who received some form of adjuvant therapy had a 5-year OS of 36±18.4 % and patients who did not receive adjuvant therapy had a 5-year OS of 85±12 % (Fig. 4d).

Table 8 Summary of adjuvant therapy in unilateral thalamic tumors

	Radiation (n=5)		Chemotherapy (n=9)		Chemotherapy and radiation (n=15)	
	At diagnosis	At progression	At diagnosis	At progression	At diagnosis	At progression
Observation only	0	0	0	0	0	0
Observation then biopsy	1	0	0	1	0	0
Observation and resection	0	0	1	0	0	0
Biopsy only	2	0	3	0	6	0
Biopsy and resection	0	0	1	1	1	0
Resection only	1	1	1	1	8	0

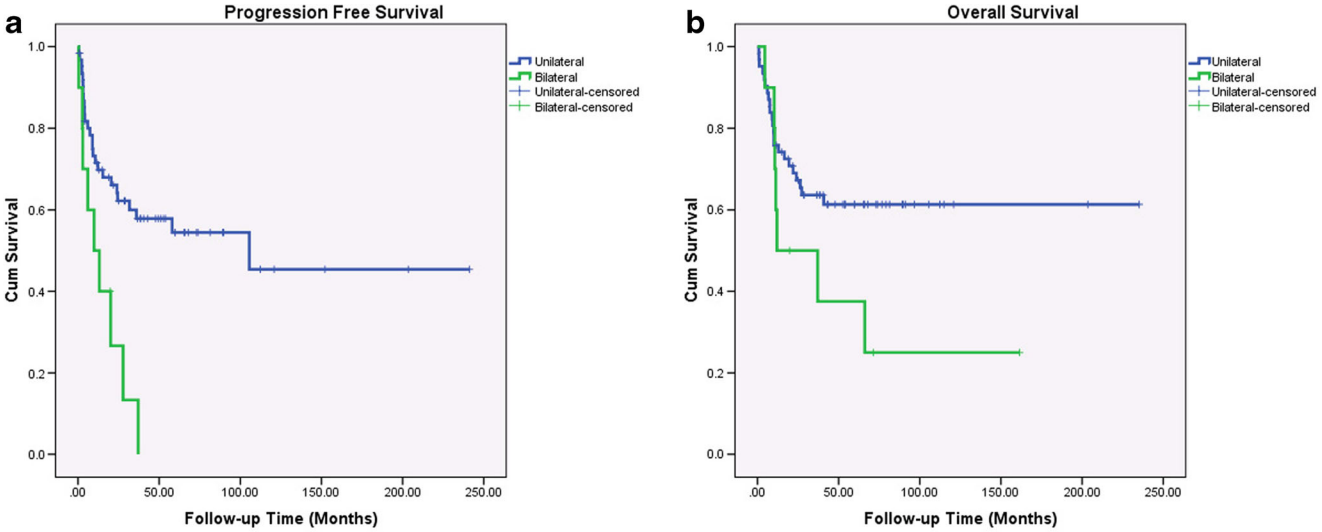

Fig. 3 Unilateral and bilateral thalamic tumor **a** 5-year progression free survival; **b** 5-year overall survival

To delineate which of these factors was most influential for survival, a multivariate, binary linear regression model was utilized (Table 10). In this model, which included tumor grade, extent of resection, symptom duration, and adjuvant therapy, tumor grade was the only significant factor in determining survival of patients with unithalamic tumors.

Bilateral thalamic tumors

Ten patients (14 %) had bilateral thalamic tumors. Six (60 %) were females and average age at presentation was 6.6 years (range: 1.5–14.7 years). The mean duration of symptoms was 2.5 months. The majority presented with symptoms of increased ICP (70 %). Other presenting signs and symptoms are detailed in Table 2. Details of presentation, radiology, treatment, and survival for each bilateral thalamic tumor are presented in Table 11.

Table 9 Factors influencing overall survival for unilateral tumors

Prognostic factor	5-year overall survival (%)	Mean overall survival (months)	*p* value
Histological finding			
Low grade	84.3±17.4 %	105.3	$p<0.001$
High grade	6.9±13.2 %	17.8	
Symptom duration			
<3 months	42.1±17.2 %	105.3	$p<0.001$
>3 months	86.4±15.0 %	179.4	
Adjuvant therapy			
Yes	35.9±18.4 %	51.1	$p=0.001$
No	84. 8±12.4 %	199.9	
Extent of resection			
0–94 % removal	52.0±16.2 %	128.3	$p=0.043$
>95 % removal	79.8±18.2 %	165.2	

Radiology (Table 3)

Bithalamic tumors were heterogeneous in 6 cases (60 %), with only 2 (20 %) showing significant contrast enhancement. None had a cystic component. All had ventriculomegaly. Two bithalamic tumors had focal calcification and 2 had perilesional edema on imaging.

Pathology

Central histopathology was available for 5 tumors. The diagnosis was diffuse astrocytoma in 3 and glioblastoma in 2 cases. An additional 4 cases had a pathology diagnosis at their home institution; however, these cases were not available for review by the central pathologist (primary site diagnosis: 2 anaplastic astrocytomas, 1 glioblastoma, and 1 pilocytic astrocytoma).

Surgery

Surgical resection was never performed for these tumors. Biopsy was done in 9 cases (90 %), ventriculoscopic in 4, stereotactic needle in 4, and open in 1 (Table 5). Two patients developed post biopsy complications which included hemorrhage and motor weakness in one patient and abnormal extraocular movements in the other. Both complications occurred after stereotactic needle biopsies. In 4 cases, the biopsy sample was not adequate for definitive diagnosis. Of the inadequate biopsies, 2 were ventriculoscopic, 1 was stereotactic needle, and 1 was both ventriculoscopic and stereotactic needle.

All bilateral tumors had ventriculomegaly on the diagnostic MRI. Seven had evidence of increased ICP and underwent treatment for hydrocephalus with ETV in 4, VP shunt in 2,

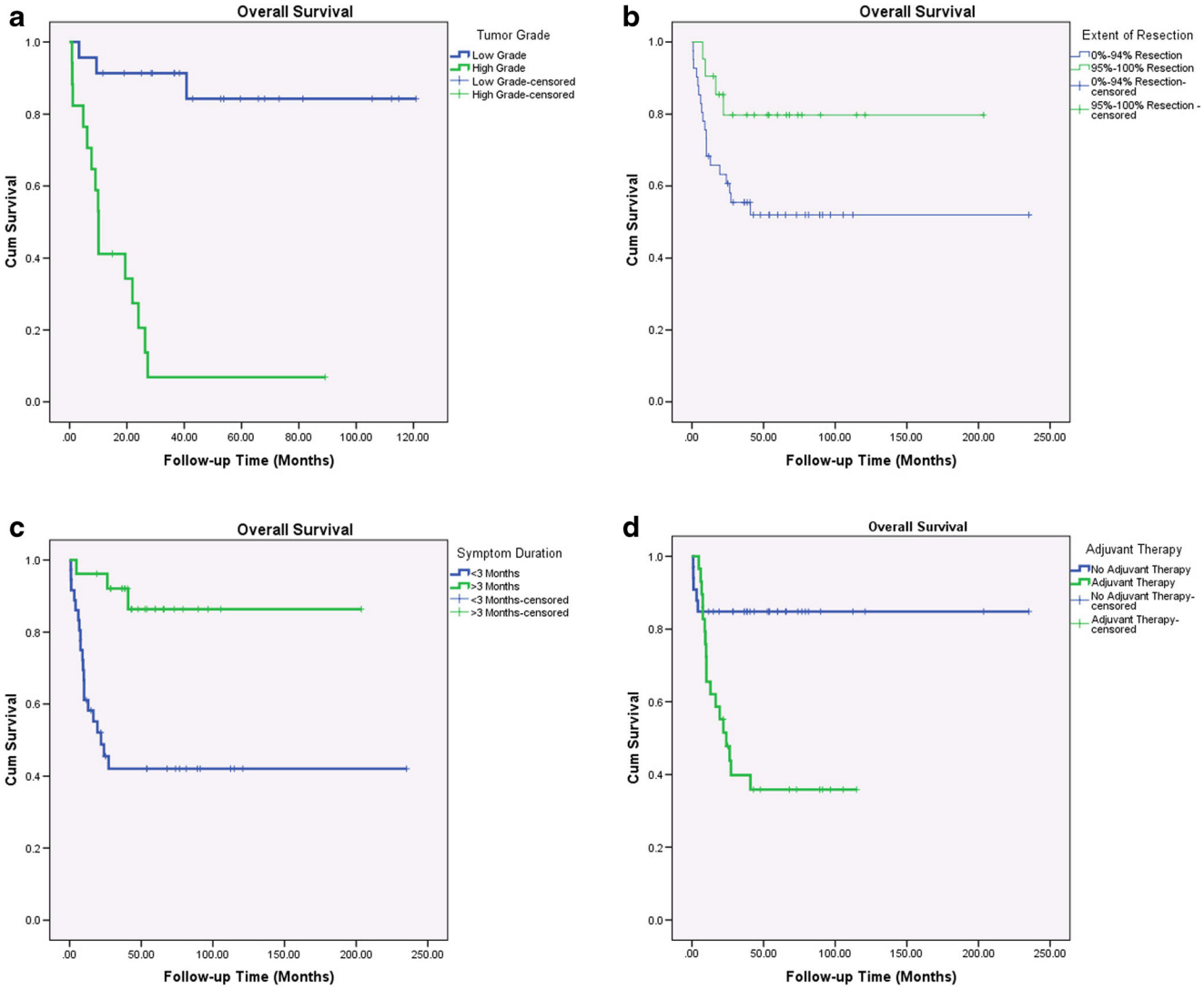

Fig. 4 Unilateral thalamic tumor overall survivals for: **a** tumor grade; **b** extent of resection; **c** symptom duration; **d** adjuvant therapy

and VP shunt with septostomy in 1. Four had a tumor biopsy at the time of their hydrocephalus surgery.

Adjuvant treatment

Adjuvant therapy was used in 7 bithalamic tumors (70 %): both chemotherapy and radiotherapy in 4, radiotherapy only in 1, chemotherapy only in 2. Overall, 6 patients underwent chemotherapy (5 as initial treatment, 1 after progression).

Chemotherapy elicited no change (<25 % change) in 2 tumors, while the remaining 4 tumors progressed despite chemotherapy at 0.4, 2.7, 9.9, and 13.2 months, respectively. Regimens used include the following: ACNS 0423 (2); Lomustine, vincristine and prednisone according to COG 945 (1); COG 9952 Regimen A (1); COG 9233 Regimen A (1); and Temozolomide followed by bevacizumab (1).

Radiotherapy was used in a total of 5 patients (3 after initial diagnosis and 2 after progression). Radiotherapy resulted in a partial response in 1 patient, stable tumor in 1 patient, and progression of the tumor in the remaining 3 patients at 0.4, 2.7, and 6 months, respectively. The median radiation tumor dose was 54.0 (53.9–57.0) Gy.

Table 10 Multivariate analysis on survival of patients with unilateral thalamic tumors

Factor	Significance of factor to model
Tumor grade	p=0.005
Symptom duration	p=0.403
Adjuvant therapy	p=0.166
Extent of resection	p=0.233

Table 11 Bilateral thalamic tumor patient summary

Patient	Clinical symptoms	Pathology	CT-MRI imaging	Months to tumor progression	Treatment received	Time to death or last FU (months)
1	Ataxia, tremors	Diffuse astrocytoma, WHO grade II	Homogeneous	6	Radiotherapy Chemotherapy	Dead (11)
2	Headache, papilledema, ataxia, learning difficulties	Diffuse astrocytoma, WHO grade II	Homogeneous	20	None	Alive (71)
3	Papilledema, memory loss, behavior changes	Glioblastoma, WHO grade IV	Heterogeneous	37.	Radiotherapy	Dead (37)
4	Headache, vomiting, tremors	n/a	Heterogeneous	3	Chemotherapy	Dead (5)
5	Convergence retractory nystagmus	n/a	Heterogeneous, calcification	28	None	Alive (161)
6	Headache, vomiting, papilledema, hemiparesis, upgaze paresis, ataxia, tremors, memory loss, behavior changes, Sleepy	Glioblastoma, WHO grade IV	Homogeneous on T1 Heterogeneous on T2	3	Radiotherapy Chemotherapy	Dead (10)
7	Headache, vomiting, papilledema	n/a	Homogeneous, calcification	20	None	Alive (20)
8	Vomiting, hemiparesis, behavior changes, dysphasia, Seizures, then coma	Oligodendroglioma, WHO grade II	Minimal edema, necrosis	13	Chemotherapy	Dead (66)
9	Headache, hemiparesis, lethargy, slurred speech	n/a	Homogeneous, extensive edema	10	Radiotherapy Chemotherapy	Dead (12)
10	Ataxia, tremor, fatigue	n/a	Heterogeneous, minimal edema	0.5	Radiotherapy Chemotherapy	Dead (11)

n/a not available

Follow-up and outcome

The average length of follow-up was 40.5 months (median 15.9 months; range 4.5 to 161.5 months). Seven patients (70 %) died during follow-up with median time to death of 11.3 months (4.6 to 66.1 months). The majority (90 %) of bithalamic tumors progressed, with the mean time to progression being 14.0 months (0.4 to 37.1 months; SD 12.1). The 5-year PFS was 0 % and 5-year OS was 37±32 % (Fig. 3). The median survival of those who received adjuvant therapy was 11.3 months (4.6 to 66.1 months). The median survival of those who received no adjuvant therapy was 71.4 months (19.9 to 161.5 months). Four patients survived longer than 3 years (Table 11: cases 2, 3, 5, and 8), and in 2 of them, no treatment was given. Those patients who presented with hemiparesis and/or tremor seemed to have a worse prognosis. The 3 patients who were survivors with no treatment presented with only evidence of raised intracranial pressure or Parinaud syndrome. Neither of the 2 patients with glioblastoma was a long-term survivor. One patient with a long survival was unusual in having a marked amount of calcification in the tumor. Due to the limited number of bilateral thalamic tumors represented in this study, further survival sub-analysis was not performed.

KIAA1549-BRAF fusion testing

Twenty-three cases had material available and RNA of sufficient quality for KIAA1549-BRAF fusion analysis. Seventeen (74 %) cases lacked a fusion event, including all tumors diagnosed as high-grade glioma or as diffuse astrocytoma and all bithalamic cases. Six cases were fusion positive, one with KIAA1549(exon15):BRAF(exon9) and five with KIAA1549(exon16):BRAF(exon9). These represented five cases diagnosed as pilocytic astrocytoma and one as low-grade astrocytoma. When one compared the 6 pilocytic and low-grade astrocytomas with BRAF fusion events with the 5 patients with similar pathologies and no fusion events (pilocyctic 4, low-grade astrocytoma 1), the mean time to tumor progression was 55.6 and 52.9 months, respectively, and all patients in both groups were alive at time of last follow-up.

Discussion

This study aimed to review and characterize multi-institutional thalamic tumor cases from the MRI era by characterizing thalamic tumors into two groups, consisting of unilateral thalamic tumors and bilateral thalamic tumors, based on MR images reviewed by a single reviewer. Bilateral tumors were defined as tumors that had involvement of both thalami, whereas unilateral tumors were defined to arise predominantly from one side of the thalamus with the epicenter in the thalamus. Thus, tumors invading the thalamus secondarily were excluded. This concept has to be considered when comparing this study to other series on thalamic tumors because other series may include tumors that do not match our definition

of thalamic tumor. In our series, 14 % of thalamic tumors were bilateral, and 86 % were unilateral. The relative frequency of unilateral versus bilateral tumors in our study closely matches other reported rates in the literature [3, 5, 8, 9].

In general, both unilateral and bilateral tumors presented with similar signs and symptoms of increased ICP and motor deficits in our series, which is concordant with previous studies [2, 5–12].

There were significant discrepancies in the pathological diagnoses on comparing the original hospital diagnosis to the central pathology review diagnosis. This is always a point of contention since treatment strategies are based on the tumor type and grade. For this reason, only pathology diagnoses that were available from central review were included in our analysis to ensure that all tumors were classified in the same manner [13–16].

Unilateral thalamic tumors

In our series, the mean age at presentation for unithalamic cases was 9.2 years, which is in keeping with prior literature on unithalamic tumors [2, 4–8, 10]. An earlier study by Cuccia et al. [2] reported a predominantly male study population, but we found no sex preponderance, which is consistent with other reported unithalamic studies [2, 4–8, 10]. The mean duration of symptoms before presentation was 8.7 months and is consistent with other reports [5, 10].

The literature suggests that unilateral thalamic tumors are predominantly astrocytomas, 33–56 % of which are high-grade lesions [4, 5, 17]. Our study's unilateral tumor group also consisted predominantly of astrocytomas (26/40), and about 43 % were high grade lesions. Seven cases (28 %) were reported as oligodendrogliomas and gangliogliomas. This is in concordance with other studies, where thalamic gangliogliomas and oligodendrogliomas have been reported to be less frequent than astrocytic tumors [1, 5, 8, 17]. In contrast, a study by Fernandez et al. reported a relatively high incidence of oligodendroglioma (~36 %) [4].

Unilateral thalamic tumors from our series predominantly exhibited contrast enhancement (61 %) and were heterogeneous on T2W MRI (68 %). In addition, 31 % of unilateral tumors in our study had perilesional edema, and 31 % were cystic in appearance. The neuroradiological findings in our study are congruent with the unithalamic imaging features described in other studies [1, 4, 5, 8]. Puget et al. noted heterogeneity in 52 %, contrast enhancement in 74 %, perilesional edema in 22 %, and cysts in 37 % in their series of 54 unilateral thalamic tumor cases [5]. Similar imaging features were noted by Fernandez et al. and Bilginer et al., although the study by Bilginer et al. did not separate bilateral and unilateral thalamic tumors [4, 8].

Diffusion weighted MR images and MR spectroscopy were not available for review. This additional information could potentially help identify radiological factors that predict pathological subtype on MRI. Pilocytic astrocytomas have been shown to have higher ADC values compared to high-grade astrocytomas [18]. MRI spectroscopy has been helpful in identifying ependymoma and differentiating between low- and high-grade glioma [19, 20]. Based on the data collected on standard MRI sequences (no diffusion scans, no spectroscopy), this study does not provide any substantial radiographic predictors of pathology.

Stereotactic biopsy is often the initial modality of management in thalamic tumors in order to obtain a pathological diagnosis. These tumors are often heterogenous, and MRI guided stereotactic biopsy may not always target representative high-grade areas within the lesion. Parts of the tumor which are non-enhancing could represent high-grade tissue. This becomes important for directing further therapy. PET using amino acid tracers can localize aggressive tumor regions as hypermetabolic and thus provides an optimum target for biopsy. Fusing PET images with preoperative MR images further increases the diagnostic yield [21]. During the time period of this study, no center in Canada used PET scans in the assessment of thalamic tumors, even as a guide for planning biopsies.

In this study, unilateral thalamic tumors predominantly extended inferiorly towards the hypothalamus, cerebral peduncle, pineal region, and midbrain. This growth pattern could potentially explain why these tumors have been often grouped along with diffuse brainstem gliomas in previous studies. It usually becomes difficult to identify the origin of the tumor when imaging shows a large lesion occupying the thalamus and upper brainstem with edema and mass effect. We had all images reviewed by a central neuroradiologist in order to clearly define tumors of thalamic origin with inferior extension and exclude brainstem gliomas.

Thalamic tumor management has evolved over time with the increasing availability of innovative surgical and neuroimaging tools, which have lessened morbidity rates associated with open biopsy and resection. Many studies suggest that total or subtotal resections improve the outcome and survival of thalamic tumor patients in comparison to those who do not undergo surgery [5, 7, 22]. In addition, surgical procedures ameliorate symptoms of increased intracranial pressure. In our study 39 unilateral thalamic tumors underwent resection, 16 were biopsied, and 7 received no surgical treatment. Gross total or near-total resections (>95 % tumor removal) were achieved in 21 patients (53.8 %), which is marginally higher than other reported series in the literature [5, 7, 8, 12].

More recent studies suggest that a near-total or gross total resection should be the ultimate goal of surgery in unilateral thalamic tumors, especially for low-grade tumors. However, the best approach to achieve this goal is not clear and depends to a large extent on the location of the tumor in the thalamus and the relationship of the tumor to critical structures [5, 8, 12,

17]. Bilginer et al. favor the anterior interhemispheric transcallosal approach for tumors located in the superior thalamus and the posterior interhemispheric parasplenial approach for posterior thalamic tumors [8]. Ozek et al. also recommend the interhemispheric transcallosal approach in patients with superior and anterior thalamic tumors [23]. In contrast, Baroncini et al. prefer the transcortical frontal approach over the transcallosal approach for tumors in the superior thalamus [6]. One study demonstrated a preference for the parieto-occipital transcortical transventricular approach or infratentorial supracerebellar route from the contralateral side and the parieto-occipital transventricular approach over the parieto-occipital transcortical transventricular approach for tumors that extended laterally [24]. For large tumors in highly functional areas or areas with poorly defined boundaries, Puget et al. suggested staged excisions of thalamic tumors [5]. In our series, the frontal transcallosal interhemispheric approach was the most utilized surgical approach for removal of unithalamic tumors. However, both the transcortical frontal and transcortical temporal approaches were also often used. In our series, surgeons also performed staged excisions in 5 cases.

More recently, the use of diffusion tensor imaging (DTI) and white matter tractography has been described as a valuable adjunct in the planning the surgical approach, which minimizes potential post-resection neurological morbidities and maximizes the chance of GTR [25–27]. Broadway et al. demonstrated with a modest sample size that DTI influenced the surgical resection in 8/10 children with thalamopeduncular tumors [25]. DTI tractography served as a valuable imaging adjunct to determine where the corticospinal tract was in relation to the tumor and allow the surgeons to plan the most appropriate surgical approach to allow sparing and avoid disrupting this important pathway [25]. Another small pediatric study demonstrated the utility of DTI in confirming the expected location of the internal capsule in thalamic tumor patients and helped plan the appropriate surgical approach for the removal of these tumors [27]. Information on DTI was not collected in our study.

Factors that influenced survival in this study on univariate analysis included tumor grade, extent of resection, adjuvant therapy, and symptom duration, which is consistent with multiple other reported series [4, 5, 7, 8, 12, 22]. Interestingly, patients who received some form of adjuvant therapy had a worse survival outcome in comparison to patients who did not receive adjuvant therapy. This probably reflects the fact that patients with more progressive and high-grade disease were more likely to receive radiation with or without chemotherapy. In our series, patients who received radiation therapy predominantly had high grade lesions (when pathology diagnosis was available). In contrast, the patients with unilateral tumors, who received chemotherapy only, predominantly had low-grade lesions with little surgical resection.

On multivariate analysis, tumor grade was the only significant factor that predicted survival in our series. To our knowledge, of the known studies on unilateral thalamic tumors in children, this series is the first to perform a multivariate analysis on factors influencing survival.

Bilateral thalamic tumors

The 10 bilateral tumors in our study represented approximately 14 % of our study population and is one of the largest pediatric cohorts bithalamic tumors published. Other reported series found similar incidences of bilateral thalamic tumors [5, 8]. The mean age at presentation was 6.6 years, which is congruent with other reported series [3, 5]. As in other reports, bilateral thalamic tumor cases had a relatively shorter mean duration of symptoms of 2.5 versus 8.7 months for unilateral thalamic tumors [3, 5, 9, 28]. In our series, bilateral thalamic tumors were predominantly heterogeneous on T2W MRI. In addition, the majority of bithalamic tumors did not exhibit contrast enhancement, which other published series also note [3, 9, 29].

Previous studies indicate that bilateral thalamic tumors are predominantly of low-grade astrocytoma histology [3, 5, 8, 9, 12, 28, 29]. Pathology was obtained in 50 % of the bilateral thalamic tumors in our series. Diffuse astrocytoma (grade II) represented 3 cases and glioblastoma 2.

Prior studies suggest that bilateral thalamic tumors are inoperable beyond diagnostic biopsy due to their location in both thalami [3, 5, 8, 12]. Our results support this notion, with none of the bilateral thalamic tumor cases in our series undergoing a surgical resection. Instead, 8 bithalamic cases received a diagnostic biopsy, and 2 were observed without biopsy. Ventriculomegaly seemed to be a sine qua non with bithalamic tumors and usually required some form of CSF diversion due to raised ICP. This is often the only surgical procedure that can be performed in these patients for symptomatic relief and this may also provide a surgical avenue for pathological diagnosis.

Bithalamic tumors have been reported to be less responsive to radiotherapy and chemotherapy treatment in comparison to unithalamic tumors [3, 5, 8, 9]. Though the majority of our bithalamic cases (70 %) received some form of adjuvant therapy, 90 % had progressive tumor growth, and 70 % died during the follow-up period. Consequently, the relative unresponsiveness to adjuvant therapy and the inability to surgically remove bilateral thalamic tumors lead to a poor outcome. The relatively poor outcome of these lesions is noted both in our series as well as in other reported series on bilateral thalamic tumors [3, 5, 8, 9, 28].

Due to their poor clinical outcome and location, bilateral thalamic tumors are suggested by some to be the diencephalic equivalent of diffuse intrinsic pontine glioma (DIPG). DIPG are considered to have the worst prognosis of all pediatric brain tumors and have limited response to both chemotherapy

and radiotherapy [30–33]. Furthermore, the location of DIPGs in the brainstem does not allow for surgical resection, and biopsies are generally not recommended, unless as part of a defined study. Although bilateral thalamic tumors share similar attributes (poor overall clinical outcome, limited response to adjuvant therapy, inability to resect, and biopsies having a limited clinical value), our series demonstrates 3 survivors, 2 of whom can be considered "long-term" survivors, with over 5 years of follow-up after initial diagnosis. Studies on DIPGs seem to demonstrate a lower survival rate, with a recent large study reporting a median OS of 10 months [31]. Bithalamic tumors in our study, although limited by a small sample size, exhibited a longer median OS (15.9 months).

KIAA1549-BRAF fusion testing

While the study was not powered to look at differences in survival between low-grade astrocytomas with and without a KIAA1549-BRAF fusion, importantly, none of the high grade or diffuse astrocytomas harbored a fusion, and there were no deaths in the fusion positive group of patients.

Strengths and limitations

There are several limitations associated with this study and what it suggests. This is a retrospective study of patients over two decades and allows for data collection errors that are inherent in retrospective methods. Although we were quite stringent with our data collection requirements, it is impossible to avoid these errors. In addition, despite multiple institutions contributing thalamic tumor cases and the time-frame covered, this study has a relatively modest sample size. We hoped to collect data on all thalamic tumor cases in Canada during our study time frame. However, due to incomplete data from some higher volume institutions, this goal could not be achieved. As a result, we cannot assume that this study population is reflective of all Canadian cases during this time period.

Conclusion

The results from this study suggest that unilateral and bilateral thalamic tumors behave differently. Surgical resection may be possible with acceptable morbidity and may improve prognosis in unilateral disease, which is often low grade. The only significant factor predicting outcome was tumor grade. Bilateral thalamic tumors have a significantly poorer prognosis, but the occasional patient does remarkably well. The efficacy of chemotherapy and radiotherapy has not been clearly demonstrated, and this needs to be considered in the discussions with the family about management. Prospective clinical trials and novel therapeutic approaches are required to improve the prognosis for malignant unilateral thalamic tumors and bilateral thalamic tumors.

Compliance with ethical standards

Funding Financial support was provided by the following organizations:

- C17 Research Network in partnership with the Childhood Cancer Canada Foundation and the Coast-to-Coast Against Cancer Foundation.
- Brain Tumor Foundation of Canada

Conflict of interest The authors have nothing to disclose.

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