Pediatric Thalamic Gliomas
An Updated Review
Avneesh Gupta, MD; Nathan Shaller, MD; Kathryn A. McFadden, MD

Neoplasms originating in the thalamus are rare overall (1% of all brain tumors); however, they comprise approximately 5% of pediatric intracranial tumors and approach 15% of all malignant pediatric intracranial tumors in some series.1–3 Prognosis, poor overall and difficult to assess in the uneven literature, is generally related to unilateral or bilateral presentations, histologic type, histologic grade, and resectability. Because of the essential functions of the thalamus and surrounding structures, as well as the difficult surgical approach to the midline, biopsy and resection were rare in the past. But with improved surgical techniques, total or partial resection is now more frequently performed, particularly for noninfiltrating, low-grade tumors.1–13 Additionally, children with even incompletely resected low-grade thalamic gliomas can have a 5-year overall survival rate greater than 80% with adjuvant chemotherapy and radiation.13,14 Therefore, histologic verification is now thought to be critical for planning treatment, and, as a result, biopsy and total/subtotal resections are much more common today than in the past.

A PubMed search using the keywords “pediatric + thalamic + glioma” yielded 45 publications with a total of 445 cases of thalamic gliomas in patients less than 18 years of age. We found only 9 substantial institutional series tabulating all encountered thalamic histologic types in children. This survey confirmed a high proportion of astrocytomas, 81% (214 of 265), of which approximately two-thirds were diffuse astrocytomas (146 of 214) and one-third were pilocytic astrocytomas (68 of 214). Of the diffuse astrocytomas, 34% (49 of 146) were low grade (World Health Organization grade II) and 55% (81 of 146) were high grade (World Health Organization grade III or IV), making the latter subgroup the largest single category of all pediatric thalamic tumors. Oligodendrogliomas and ependymomas (mostly anaplastic in both cases) comprised 10% and 3% of all pediatric thalamic tumors, respectively.

Conclusions.—Tissue diagnosis is now thought crucial for prognostication and treatment, particularly as more potentially therapeutic molecular targets are discovered. Secure diagnosis allows identification of tumors for which resection is more feasible and beneficial.


EPIDEMIOLOGY

A PubMed search using the keywords “pediatric + thalamic + glioma” yielded 45 publications with a total of 445 cases of thalamic gliomas in patients less than 18 years of age (mean, approximately 9 years; range, 4.8–11.5 years). Of these publications, 20 were case series (Table).1,4–22 Histologically, the vast majority (70%–90%) of reported thalamic tumors are classified as astrocytoma. However, this literature is limited and difficult to interpret regarding histologic subtypes in children, as many studies combine age groups, are confined to more specific entities (eg, pilocytic astrocytoma (PA) or “high-grade astrocytoma”), group biologically distinct entities (eg, PA and low-grade diffuse astrocytoma [DA] as “low-grade astrocytoma”), or are single case reports. There is a particularly disproportionate emphasis on the striking but extremely rare bilateral diffuse thalamic astrocytoma. In our review, we found only 9 substantial institutional series tabulating all encountered thalamic histologic types in children (Table).* In this more limited series, our survey confirmed a high proportion of astrocytomas, 81% (214 of 265), of which approximately two-thirds were DAs (146 of 214) and one-third were PAs (68 of 214). Of the DAs, 34% (49 of 146) were low grade (World Health Organization [WHO] grade II) and 55% (81 of 146) were high grade (WHO grade III or IV), making the latter subgroup the largest single category of all pediatric thalamic tumors.

* References 4, 6, 7, 9, 10, 12, 13, 16, 17.
thalamic tumors. Oligodendrogliomas and ependymomas (mostly anaplastic in both cases) comprised 10% and 3% of all pediatric thalamic tumors, respectively. The remaining 6% included primitive neuroectodermal tumor, neurocytoma, and ganglioglioma.

**Pilocytic Astrocytoma**

Pilocytic astrocytoma is the most common glioma in the pediatric population and accounts for 33% of all glial neoplasms, including thalamic tumors, between the ages of 0 and 14 years. Radiologically, PAs present in the thalamus as relatively circumscribed, cystic or solid, often exophytic, and strongly and diffusely contrast enhancing masses (Figure 1, A). This corresponds to a gross appearance of discrete gray lesions with frequent intratumoral or peritumoral cyst formation. Histologically, they have characteristic biphasic architecture (Figure 1, B) with alternating compact areas showing bland bipolar glial cells and variable Rosenthal fibers (Figure 1, C) and more loose areas with multipolar cells, microcysts (Figure 1, D), and occasional eosinophilic granular bodies (Figure 1, E). The Ki67 proliferation rate is typically quite low and the vast majority

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. Thalamic Cases/Total No. Cases</th>
<th>Mean Age, y</th>
<th>Laterality</th>
<th>Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franzini et al,15 1994</td>
<td>32/70</td>
<td>47</td>
<td>Thalamic</td>
<td>Diffuse or nodular differentiation based on adjacent tissue labeling for S phase (LI) using p3-H thymidine</td>
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<tr>
<td>Cuccia et al,4 1997b</td>
<td>26/26</td>
<td>9.2</td>
<td>Unilateral</td>
<td>9 A, 9 AA, 2 AO, 4 AE, 2 GBM</td>
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<td>Gajjar et al,3 1997</td>
<td>20/142</td>
<td>7</td>
<td>Thalamic</td>
<td>7 DA, 9 JPA, other as grade IV in 4/20</td>
</tr>
<tr>
<td>Nishio et al,6 1997b</td>
<td>20/20</td>
<td>24.5</td>
<td>Thalamic</td>
<td>2 PA, 7 DA, 7 AA, 4 GBM</td>
</tr>
<tr>
<td>Reardon et al,7 1998b</td>
<td>36/36</td>
<td>10</td>
<td>24 unilateral, 12 bilateral</td>
<td>Unilateral: 15 LGA, 9 HGA; bilateral: 9 LGA, 3 HGA</td>
</tr>
<tr>
<td>Di Rocco and Iannelli,8 2002</td>
<td>4/4</td>
<td>6.4</td>
<td>Bilateral</td>
<td>3 DA, 1 AA</td>
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<tr>
<td>Ozek and Ture,9 2002b</td>
<td>18/18</td>
<td>2–16 (range)</td>
<td>Thalamic</td>
<td>10 LGA, 3 HGA, 2 E, 2 PNET, 2 GG</td>
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<tr>
<td>Allbright,10 2004b</td>
<td>19/19</td>
<td>8</td>
<td>Thalamic</td>
<td>5 PA, 1 O, 1 OA, 7 AA, 5 GBM</td>
</tr>
<tr>
<td>Peters et al,11 2004</td>
<td>4/32</td>
<td>10.3</td>
<td>Thalamic</td>
<td>5 PA, 1 O, 6 AO, 2 GBM</td>
</tr>
<tr>
<td>Fernandez et al,16 2006b</td>
<td>14/14</td>
<td>8.1</td>
<td>Unilateral thalamic</td>
<td>4 O</td>
</tr>
<tr>
<td>Puget et al,12 2007b</td>
<td>69/69</td>
<td>9.5</td>
<td>54 unilateral, 6 thalamopeduncular, 9 bilateral</td>
<td>Unilateral: 9 PA, 7 LGA, 17 HGA, 2 PNET, 2 N, 2 GG; thalamopeduncular: 4 PA, 1 HGA; bithalamic: 1 PA, 5 LGA, 1 HGA, 1 O, 1 AO</td>
</tr>
<tr>
<td>Sainte-Rose et al,17 2010b</td>
<td>83/83</td>
<td>9.5</td>
<td>Thalamic</td>
<td>18 JPA, 19 DA, 7 O, 3 GG, 29 AA/GBM, 3 AO, 3 PNET, 1 N</td>
</tr>
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<td>Kramm et al,1 2011</td>
<td>99/99</td>
<td>11.5</td>
<td>31 thalamic alone, 38 thalami and diencephalon, 30 thalami and cerebral cortex</td>
<td>61 AA, 32 GBM, 3 anaplastic PA, 3 AO</td>
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<tr>
<td>Bilginer et al,11 2014b</td>
<td>45/45</td>
<td>11.06</td>
<td>Thalamic; 37 unilateral, 8 bilateral</td>
<td>Unilateral: 14 PA, 2 AA, 11 GBM, 1 AE, 1 AO, 1 PNET, 1 GG, 2 E; bilateral: 3 PA, 1 ATRT</td>
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<td>Broniscer et al,18 2016</td>
<td>11/11</td>
<td>4.8</td>
<td>Bithalamic</td>
<td>1 DA, 8 AA, 2 GBM</td>
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<td>Pages et al,19 2016</td>
<td>2/54</td>
<td>8</td>
<td>Thalamic</td>
<td>2 GB with H3K27M mutation and BRAF V600E mutations</td>
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<tr>
<td>Ryall et al,20 2016</td>
<td>64/64</td>
<td>9.25</td>
<td>Thalamic</td>
<td>23 PA, 3 GG, 2 DA, 14 LGA, 9 AA, 11 GBM, 2 HGA; 5 low grade and 11 high grade positive for H3K27 mutation</td>
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<tr>
<td>Solomon et al,20 2016</td>
<td>23/47</td>
<td>14</td>
<td>Thalamic</td>
<td>15 of 23 cases had H3K27 mutation. Mutants: 1 DA, 4 AA, 10 GBM</td>
</tr>
<tr>
<td>Steinbok et al,21 2016</td>
<td>72/72</td>
<td>8.9</td>
<td>Thalamic; 62 unilateral, 10 bilateral</td>
<td>Unilateral: 42 cases were reviewed; 12 PA, 4 DA, 2 GG, 2 E, 2 N, 2 pilomyxoid astrocytoma, 9 AA, 3 GBM, 1 AG, 1 germinoma Bithalamic: 1 PA, 3 DA, 2 AA, 3 GBM, 1 O</td>
</tr>
<tr>
<td>Aboian et al,22 2017</td>
<td>9/9</td>
<td>9.5</td>
<td>Thalamic; 8 unilateral, 1 bilateral</td>
<td>6 cases had H3K27M mutation</td>
</tr>
</tbody>
</table>

Abbreviations: A, astrocytoma; AA, anaplastic astrocytoma; AE, anaplastic ependymoma; AO, anaplastic oligodendroglioma; ATRT, atypical teratoid rhabdoid tumor; DA, low-grade diffuse astrocytoma; E, ependymoma; GBM, glioblastoma; GG, ganglioglioma; HGA, high-grade astrocytoma; JPA, juvenile pilocytic astrocytoma; LGA, low-grade astrocytoma; LI, labeling index; N, neurocytoma; O, oligodendroglioma (low grade); OA, oligoastrocytoma; PA, pilocytic astrocytoma; PNET, primitive neuroectodermal tumor.

a Laterality not mentioned.

b Unbiased major series of pediatric thalamic tumors.
are designated WHO grade I. Occasional PAs may exhibit rare mitoses, benign nuclear atypia, glomeruloid vascular proliferation (Figure 1, F), and infarcted-type necrosis, features that do not denote a higher grade but may be alarming on a small biopsy. Markedly increased mitotic activity, nuclear anaplasia, and palisading necrosis, however, do favor a diagnosis of anaplastic pilocytic astrocytoma (WHO grade III).

Unfortunately, most large-scale studies reporting outcomes of patients with thalamic PA pool their data with DA (WHO grade II) into an unhelpful and biologically meaningless “low-grade glioma” category. Overall, extent of resection and low grade are most correlated with improved outcome, and 5-year survival appears to be approximately 40% across these studies. In the few reports where PA was treated separately, researchers observed more than 90% long-term survival in both completely and partially resected thalamic PA, indicating that survival for the well-circumscribed and indolent PA is likely much higher than that reported for low-grade gliomas.

Whole-genome sequencing studies have revealed the genetic alterations of PA converge on the mitogen-activated protein kinase (MAPK) signaling pathway. The most frequent alteration is KIAA1549:BRaf kinase fusion, seen in 60% to 70% of cases, particularly in the posterior fossa. Other observed mutations include other BRAf fusions, BRAf-v600E point mutation, various FGFR1 mutations, NTRK-family fusions, NFI mutations, or KRAS mutations. These serve to activate the MAPK signaling pathway, and any of these alterations may be at least theoretically observed in PAs arising in the vicinity of the third ventricle. Interestingly, H3.3K27 mutations have been found in very rare pediatric thalamic gliomas exhibiting pilocytic morphology and having MAPK-related alterations. This occurrence is associated with variably reduced survival.

DIFFUSE ASTROCYTOMA

In our review of the epidemiologically unbiased literature, DA comprises approximately 68% (146 of 214) of thalamic astrocytomas and 55% (146 of 265) of all thalamic tumors in children. As mentioned, 34% (49 of 146) of all DAs were low grade (WHO grade II) and 66% (81 of 146) were high grade (WHO grade III or IV). Still, it is possible that the incidence is underestimated in older series, as empiric treatment of histologically unconfirmed diffuse tumors was more common in the past. Radiologically, the lesions appear heterogeneous but minimally enhancing, and extend to nearby structures (Figure 2, A). Histologically, DAs of the thalamus are identical in their features and broad morphologic variation to those occurring elsewhere and are graded in the same manner. Low-grade tumors typically exhibit naked-appearing hyperchromatic glial nuclei, with at most moderate pleomorphism, infiltrating normal parenchymal elements (Figure 2, B). High-grade DAs exhibit increased hypercellularity (Figure 2, C) and nuclear anaplasia, and are mitotically active (WHO grade III) with or without palisading necrosis, endothelial proliferation, and thrombosis (glioblastoma, WHO grade IV) (Figure 2, D).
Thalamic DA carries a dismal prognosis in general. Histologic grade and extent of resection are traditionally the most often cited key prognostic factors, as it is all but impossible to resect an infiltrating tumor at this location. However, the outcome literature is varied and difficult to interpret. More circumscribed gliomas with a low Ki67 proliferation rate and significant resection appear to average 40% to 50% 5-year survival, particularly if substantially resected. However, it is likely that much of the perceived benefit of resection (and possibly grade) is conferred by the significant number of PAs included in most samples as well as the difficulty of distinguishing between PA and low-grade DA in small biopsies. Five-year survival rates for high-grade thalamic DA have tended to average 15% to 25% in the literature, although these numbers are quite variable. Moreover, recent studies have indicated that extent of resection may not be as prognostically important as originally believed, particularly in high-grade and/or bithalamic DA, which suggests that additional biologic factors related to thalamic location may be influencing outcome.

Despite their histologic similarities, pediatric infiltrating gliomas arise frequently within the pons and thalamus and are unlikely to harbor the alterations of IDH1, IDH2, EGFR, PTEN, and ATRX that are common in adult DA. Methylation of the methylguanine methyltransferase gene (MGMT) and p53 overexpression have been identified in a subset of high-grade infiltrating thalamic gliomas that, along with elevated proliferation, appear to correlate with particularly poor outcome. Recently, H3K27M mutations have been detected in a significant subset (65%–90%) of high-grade pediatric and young adult thalamic DAs, placing them firmly in the genetically defined category of diffuse midline glioma. These tumors are defined by the

Figure 2. Imaging and microscopic features of diverse thalamic diffuse astrocytomas. A, Magnetic resonance imaging T2 fluid attenuation inversion recovery showing massive bilateral thalamic expansion. B, Thalamic biopsy showing low-grade (World Health Organization [WHO] grade 2) diffuse astrocytoma. C, Example of more hypercellular anaplastic (WHO grade 3) diffuse thalamic astrocytoma. D, Diffuse thalamic astrocytoma meeting criteria for glioblastoma with abundant vascular proliferation (arrowhead) (hematoxylin-eosin, original magnification ×200 [B through D]).

† References 1, 4, 6–9, 12, 13, 15, 18, 19, 31, 32.
WHO Classification of Tumors of the Central Nervous System as an infiltrative midline high-grade glioma with predominantly astrocytic differentiation and a K27M mutation in either H3F3A or HIST1H3B/C, and are automatically graded as WHO grade IV.

Subsequently, Ishibashi et al reported H3K27M mutation detected in a pediatric thalamic glioma both at first biopsy, when it was histologically low grade, and at recurrence, when it was diagnosed as anaplastic astrocytoma. Ryall et al detected H3K27M mutations within 12% (5 of 42) of low-grade and 50% (11 of 22) of high-grade thalamic gliomas. Even lower-grade tumors harboring H3K27M mutations had a dismal median survival of approximately 1 year. These findings, as well as low intratumoral heterogeneity, indicate H3K27M mutation is an early event in midline glioma tumorigenesis. A highly specific antibody is available for detecting H3K27M that is extremely helpful in recognizing this alteration in limited biopsies. Interestingly, low- and high-grade bithalamic gliomas have been thus far negative for H3K27M mutations, suggesting this is a molecular entity distinct from unilateral H3K27M–mutated thalamic glioma.

Figure 3. Microscopic features of thalamic oligodendroglioma. A, Moderately cellular tumor showing relatively monotonous rounded nuclei, clear cytoplasm, and distinct cell borders in a mucoid background. B, Another example with a more fibrillary background. C, Similar clear cell tumor showing perivascular clearing and microcalciﬁcation (arrowhead). D, Round cell tumor with arborizing, hyalinized vessels and perivascular clearing. None of these tumors showed immunohistochemical or molecular evidence of ependymal differentiation (hematoxylin-eosin, original magnifications ×200 [A, B, and D] and ×400 [C]).
THALAMIC/CENTRAL OLIGODENDROGLIOMA

In our review, approximately 10% of thalamic gliomas were histologically compatible with a diagnosis of oligodendroglia. Typically, these tumors are composed of monotonous round cells with round to ovoid nuclei, clear cytoplasm, and relatively distinct cell borders (Figure 3, A through D). Arborizing capillaries and at least focal microcalcifications (Figure 3, C) are usually present. Neurocytoma, clear cell ependymoma, and PA with oligodendrogli-like cells are possible diagnostic challenges in small biopsies. Approximately 60% of these tumors had additional features of nuclear atypia, increased mitotic rate, necrosis, and/or endothelial proliferation necessitating a diagnosis of anaplastic oligodendroglioma, WHO grade III.

Interestingly, a number of authors have singled out thalamic or “central” oligodendroglioma as being biologically distinct both from diffuse thalamic astrocytomas of a comparable grade and from peripheral (hemispheric) pediatric oligodendrogliomas of a comparable grade.\(^6,7,11,16,26,39\) Thalamic oligodendrogliomas are often anaplastic at biopsy/resection and relentlessly progress (14% 3-year survival in one series) despite extent of resection or chemotherapy and radiation in a manner comparable with thalamic glioblastoma.\(^6\) Surprisingly, low-grade (WHO grade II) thalamic oligodendrogliomas have a similarly dismal prognosis. Although samples are small, various reports indicate overall survival times range from 12 to 24 months.\(^3,12,26,39\)

Difficulty of resection clearly plays a role in these statistics; however, the thalamic location may also impart a distinct biology to these tumors. As with pediatric oligodendroglia, the thalamic variant is not IDH1/2 mutated or 1p/19q codeleted. However, the majority with reported molecular data, including one case from our own institution (not reported), show at least partial loss or other alterations of 1p,\(^16\) a finding only rarely seen in hemispheric pediatric oligodendrogliomas.\(^40-42\) It is unknown how many, if any, pediatric thalamic oligodendrogliomas exhibit concurrent H3.K27 mutations, although Solomon et al\(^20\) report H3.K27 mutations in a hypothalamic tumor with oligodendroglial morphology.

EPENDYMOMA

Ependymoma is the third most common brain tumor (10%) in the pediatric population, with approximately one-third occurring in the supratentorial compartment. These may be associated with the ventricles or arise from extraventricular locations such as cortex, subcortical white matter, or deep gray matter. In our review, ependymomas comprised approximately 3% of thalamic tumors, although single case studies abound in the literature. Ependymomas are considered noninfiltrative tumors and are generally well circumscribed. Histologically, they are typically composed of unipolar and bipolar spindle-shaped glial cells with ovoid nuclei with lightly speckled chromatin. There are perivascular anuclear zones (perivascular pseudorosettes) (Figure 4, A and B) and occasionally true ependymal rosettes that resemble the normal ependymal canal. They are considered WHO grade II unless anaplasia, increased mitotic activity endothelial proliferations, and/or necrosis are present (Figure 4, C), in which case a diagnosis of anaplastic ependymoma, WHO grade III, is rendered, although clinical behavior is not well predicted by grade.

One variant, clear cell ependymoma, preferentially arises within the supratentorial compartment and is the most common histopathologic pattern of intraparenchymal midline supratentorial ependymomas in children.\(^43,44\) These tumors are characterized by sheets of uniform cells with round, central nuclei, perinuclear halos, conspicuous cell borders, and a prominent arborizing capillary network (Figure 4, D through F) closely mimicking oligodendrogli-
oma, also a diagnostic consideration in the thalamus. A large proportion are anaplastic and exhibit rapid disease progression and rare extraneural metastases. All have at least partial trisomy 19, C11orf95-RELA fusion, and CDKN2A (9p21.3) deletions, which are associated with poor prognosis.\textsuperscript{45,46}

The primary treatment for ependymoma is surgical resection followed by radiotherapy. The most consistently important prognostic factor is extent of surgical resection, with gross total resection often curative. Chemotherapy remains largely ineffective. However, an estimated 40\% of ependymomas are incurable, particularly when located in the lateral posterior fossa or deep gray structures such as the thalamus.\textsuperscript{47} Additionally, a large percentage of supratentorial ependymomas, even those without clear cell histology, carry C11orf95-RELA fusion and CDKN2A (9p21.3) deletion. Although gross total resection is usually not possible in the thalamus, subtotal or partial resection of these relatively circumscribed tumors is occasionally possible and may improve prognosis.

**SUMMARY**

Despite being uncommon overall, thalamic tumors comprise a substantial subset of malignant intracranial tumors in children. Improved neurosurgical techniques have made safe biopsy and surgical resection possible for these once uncommon neuropathologic specimens. In fact, tissue diagnosis is now thought crucial for prognostication and treatment planning, particularly as more potentially therapeutically targets are discovered. Secure diagnosis allows identification of tumors for which resection is more feasible and beneficial. In one stereotactic biopsy study of thalamic lesions,\textsuperscript{48} approximately 18\% of cases were actually nonneoplastic. One particularly important subset of thalamic tumors to identify is the malignant diffuse midline glioma. They display a remarkable morphologic diversity, and H3K27M-mutated tumors may appear quite bland or display ependymal, pilomyxoid, pleomorphic xanthoastrocytoma-like, or primitive neuroectodermal features.\textsuperscript{49} Therefore, H3K27M detection should be performed on all thalamic tumors, at least by immunohistochemistry.

**References**


