Long-term clinical and visual outcomes after surgical resection of pediatric pilocytic/pilomyxoid optic pathway gliomas

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OBJECTIVE The choice of treatment modality for optic pathway gliomas (OPGs) is controversial. Chemotherapy is widely regarded as first-line therapy; however, subtotal resections have been reported for decompression or salvage therapy as first- and second-line treatment. The goal of this study was to further investigate the role and efficacy of resection for OPGs.

METHODS A retrospective chart review was performed on 83 children who underwent surgical treatment for OPGs between 1986 and 2014. Pathology was reviewed by a neuropathologist. Clinical outcomes, including progression-free survival (PFS), overall survival (OS), and complications, were analyzed.

RESULTS The 5- and 10-year PFS rates were 55% and 46%, respectively. The 5- and 10-year OS rates were 87% and 78%, respectively. The median extent of resection was 80% (range 30%–98%). Age less than 2 years at surgery and pilomyxoid features of the tumor were found to be associated with significantly lower 5-year OS. No difference was seen in PFS or OS of children treated with surgery as a first-line treatment compared with children with surgery as a second- or third-line treatment. Severe complications included new disabling visual deficit in 5%, focal neurological deficit in 8%, and infection in 2%. New hormone deficiency occurred in 22% of the children.

CONCLUSIONS Approximately half of all children experience a long-term benefit from resection both as primary treatment and as a second-line therapy after failure of primary treatment. Primary surgery does not appear to have a significant benefit for children younger than 2 years or tumors with pilomyxoid features. Given the risks associated with surgery, an interdisciplinary approach is needed to tailor the treatment plan to the individual characteristics of each child.

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KEYWORDS optic pathway gliomas; pilocytic/pilomyxoid astrocytomas; clinical outcomes; surgical resection; complications; oncology

Optic pathway gliomas (OPGs) are a spectrum of lesions that account for about 5% of pediatric brain tumors,12,29 with 75% involving multiple portions of the optic pathways.30 Most OPGs are classified histologically as pilocytic astrocytoma (PA), a typically benign tumor;11,30 A minority are classified as pilomyxoid astrocytoma (PMXA), a variant that seems to be correlated with worse survival.13,28 After radiological diagnosis, children may be monitored with watchful waiting since some tumors remain stable or are minimally progressive.4,20 In rare cases, spontaneous regression without treatment has been observed.26 Historically, radiation therapy was the standard treatment for OPGs, but deleterious long-term effects of cerebral radiation in the pediatric population24 have pushed physicians to find alternative treatments to delay or avoid the use of radiation. Chemotherapy has been established as the first-line therapy with multiple treatment protocols; new molecular targeted drugs are also being investigated for second-line and possibly primary therapy.3,18,19,30,31,34
The role of surgery in the treatment of OPGs is unclear. A few centers have advocated primary resection for exophytic tumors; however, resection has been mainly considered as a second-line treatment for tumor progression. Surgery as first-line treatment is controversial in lesions that have significant exophytic components in addition to the diffuse involvement of the chiasm or hypothalamus. Gross-total resection cannot be achieved due to the infiltrative component of the tumor involving the chiasm and hypothalamus. Subtotal resection (STR) has shown promising short-term results in children with these exophytic hypothalamic/chiasmatic tumors; however, more data are needed on complications and long-term outcomes of these benign tumors. A prospective series of pediatric patients with midline-chiasmatic, low-grade gliomas reported a 5-year PFS of 53% after STR. There have also been reports of regression of OPGs after surgery without adjuvant treatment.

This study examines the clinical and visual outcomes of 83 children with OPGs who were operated on by the senior author (J.H.W.) as a first-line or second-line treatment. The goal was to further investigate the role and efficacy of resection in the treatment of OPGs.

Methods

We conducted an institutional review board–approved retrospective chart review of patients with a radiological diagnosis of optic pathway tumors that were resected between 1986 and 2014. Patients were identified from the surgeon’s database and a pathology database. All patients treated with resection by the senior author (J.H.W.) who were younger than 21 years at the time of diagnosis and had a pathologic diagnosis of PA or PMXA were included in the study. The data were collected through electronic medical records, office charts, operative reports, and MRI scan results. The following variables were analyzed: clinical history and diagnosis, presenting symptoms, neurological and visual deficits, neuroimaging, number of operations, adjuvant therapy, perioperative complications, visual outcomes, progression, and survival information.

Resection was performed as either primary treatment without adjuvant treatment or management of exophytic disease after tumor progression if first-line treatment failed. We excluded children who had a diagnostic biopsy as their only procedure. Indications for primary resection included 1) exophytic tumor mass causing progression of endocrine, neurological, or visual deficit; 2) relief of raised intracranial pressure caused by the tumor volume; and 3) resection of a third ventricle tumor and relief of hydrocephalus. The indications for surgery as a salvage therapy after failure of first-line treatment were similar to those for primary resection. The goal of the surgery in all cases was maximal safe resection of the exophytic, extrinsic component of the tumor, which, depending on the characteristics of the tumor, resulted in different rates of STR.

The children included in this study were classified into 2 treatment groups. Patients in group 1 were treated primarily with surgery without adjuvant therapy, and those in group 2 had undergone treatment (chemotherapy, surgery, or radiation therapy) prior to presenting to the senior author and underwent salvage surgery. Those who had first-line surgery followed by immediate planned adjuvant therapy were not included in this study.

Radiological Classification

The presurgical radiological images of the patients were retrospectively reviewed by 2 pediatric neurosurgeons (J.H.W. and E.T.H.) and classified according to the modified Dodge classification. This classification defines tumors as involving the optic nerves alone (stage 1), the chiasm with or without nerve involvement (stage 2), or involving the hypothalamus or other adjacent structures (stage 3). An additional clinico-radiographic classification was utilized to describe patterns of growth and optimal trajectory for surgical intervention. The floor of the third ventricle is the reference ground for this classification. Type 1 (anterior inferior) includes lesions that extend into the suprasellar and adjacent cistern, occasionally extending subfrontally. Type 2 includes lesions with predominant growth superior and posterior filling the third ventricle. Type 3 are tumors with extensive growth in both directions.

Surgical Outcomes and Complications

The extent of resection was defined as the percentage decrease in volume of the lesion on postoperative MRI compared with that on preoperative MRI and confirmed by imaging 2–3 months after surgery. The aim of the surgery was never a gross-total resection due to the infiltrative intrinsic component of OPGs involving the chiasm and the hypothalamus. The medical records were reviewed, and complications were classified as new and permanent disabling visual deficit, new nondisabling visual deficit, new and permanent focal neurological deficit, new transient focal neurological deficit, infection, or new hormone deficit. New disabling visual deficits included decreased vision in both eyes, new hemianopia, and blindness in one eye or both eyes. New nondisabling visual deficits were defined as new quadrantanopia or decreased visual acuity in one eye.

Pathology

At the time of this study, tissue from surgery was obtained from the New York University Center for Biospecimen Research and Development for all patients. All H & E slides for each case were reviewed by a board-certified neuropathologist (M.S.) to confirm the diagnosis according to the WHO. Tumors were categorized as a PA, PMXA, or pilocytic astrocytoma with pilomyxoid features (PA/PMXA) as previously described. Patients with tumors that had a different histology were excluded from this study.

Follow-Up

Progression was defined as an at least 10% increase in volume compared with the volume on immediate postoperative MRI. Date of progression was the date the imaging was performed. Progression-free survival (PFS) was determined as the time from surgery to radiographic progression.
Preoperative and postoperative visual status was determined for all patients by ophthalmological evaluation and/or evaluation by the pediatric neurosurgeon. Children were determined to have normal, impaired, or no vision preoperatively. Postoperative vision was then determined on the last follow-up visit by ophthalmological evaluation and/or evaluation by the neurosurgeon. Long-term visual outcomes were classified as improved, stable, or worse.

Statistical analyses were run on GraphPad Prism 7 for Mac OS X. Data were compared using Fisher’s exact tests, Welch’s t-tests, and Kaplan-Meier curves. Statistical significance was considered as p < 0.05.

Results

A total of 116 patients were identified to have undergone surgery by the senior author for an optic pathway tumor. Eighty-three children met the inclusion criteria and are reported on in this study. The demographics are summarized in Table 1. The mean and median lengths of follow-up after surgery were 10 and 8 years, respectively (range 0–32 years). Of the 65 long-term survivors, 52 children (80%) had a follow-up of 5 years or more and 39 children (60%) had a follow-up of 10 years or more.

Presenting Symptoms

The most common presenting symptoms were neurological deficit and visual impairment, which were seen in 37 children (45%) and 29 children (35%), respectively. Children also presented with headaches (18 children, 22%), diencephalic syndrome (13 children, 16%), and hormonal disturbance (11 children, 13%). Three children (4%) were diagnosed with an OPG serendipitously due to imaging for other reasons.

Treatment Pathways

Surgery was performed in 37 children as first-line treatment (group 1) and in 46 children as second- or third-line treatment (group 2) (Fig. 1). Children in group 1 were diagnosed at an older age (p = 0.04) and were taken to surgery more quickly after diagnosis (p < 0.0001) than those in group 2. Age at surgery was not different between the 2 groups (p = 0.2; Table 1). Children in group 1 were more likely to have Dodge stage 2 tumors (p = 0.04). PFS (p = 0.2) and overall survival (OS) (p = 0.5) were not shown to be significantly different between the 2 treatment pathways (Fig. 2).

Overall PFS and OS

The overall 5- and 10-year PFS rates were 55% and 46%, respectively. The overall 5- and 10-year OS rates were 87% and 78%, respectively. When comparing children who were operated on during the first part of the study (1986–1999) versus the last part of the study (2000–2014), there was no significant difference in 5- and 10-year PFS or OS: 5-year PFS in the first time frame was 63% and in the second time frame was 48% (p = 0.2); 5-year OS in the first time frame was 83% and in the second time frame was 90% (p = 0.5) (Supplemental Fig. 1). There was no difference in overall PFS and OS with regard to patient sex.

Age at Surgery

There was a statistically significant difference in OS with regard to age at surgery. At 20 years of follow-up,

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**Table 1. Characteristics of children in the study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 83)</th>
<th>Group 1 (n = 37)</th>
<th>Group 2 (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>4 (0–20)</td>
<td>6 (0–20)</td>
<td>3.5 (0–20)</td>
</tr>
<tr>
<td>At op</td>
<td>7 (0–30)</td>
<td>6 (0–24)</td>
<td>7.5 (1–30)</td>
</tr>
<tr>
<td>Median yrs from diagnosis to op (range)</td>
<td>1 (0–16)</td>
<td>0 (0–16)</td>
<td>4 (0–16)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41 (49)</td>
<td>18 (49)</td>
<td>23 (50)</td>
</tr>
<tr>
<td>Male</td>
<td>42 (51)</td>
<td>19 (51)</td>
<td>23 (50)</td>
</tr>
<tr>
<td>Positive NF1 status, n (%)</td>
<td>8 (10)</td>
<td>4 (11)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Pathology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>71 (86)</td>
<td>32 (86)</td>
<td>39 (85)</td>
</tr>
<tr>
<td>PMXA</td>
<td>7 (8)</td>
<td>3 (8)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>PA/PMXA</td>
<td>5 (6)</td>
<td>2 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Tumor location*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dodge stage 2</td>
<td>7 (9)</td>
<td>6 (16)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dodge stage 3</td>
<td>75 (91)</td>
<td>31 (84)</td>
<td>44 (98)</td>
</tr>
</tbody>
</table>

* Information to assess the Dodge stage was not available in 1 patient in group 2.
patients who were diagnosed and had surgery at 2 years or older were more likely to survive than those who were initially diagnosed and operated on while younger than 2 years (p = 0.03) (Fig. 3).

Pathology
Seventy-one children (86%) had tumors classified as PA, and 12 children (14%) were diagnosed as being part of the pilomyxoid group (PMXA or PA/PMXA). There was a trend toward longer PFS in patients with PA than in patients with tumors with any pilomyxoid features, with 5-year PFS of 59% and 33%, respectively (p = 0.1). There was a longer 5-year OS for patients with PA (90%) than for those in the pilomyxoid group, 67% (p = 0.05); however, long-term OS was not statistically significant (Fig. 4).

Extent of Resection
The median extent of resection was 80% (range 30%–98%). There was no significant difference in the extent of resection between children without tumor progression (median 80%, range 30%–98%) and children with tumor progression (median 75%, range 40%–95%) (p = 0.4). There was also no significant difference in the extent of resection between survivors (median extent of resection 80%, range 45%–98%) and nonsurvivors (median extent of resection 70%, range 30%–95%) (p = 0.1) (Supplemental Fig. 2).

Complications
Severe complications were disabling visual deficit in 4 (5%), focal neurological deficit in 7 (8%), and infection in 2 children (2%). New hormone deficiency occurred in 18 children (22%) (Table 2).

There was no correlation between age at surgery, group, location of tumor, extent of resection, and complications overall. There was no correlation between severe complication, new permanent focal neurological deficit, or new hormonal deficit and age at surgery, extent of resection, treatment prior to surgery, or location of tumor (Table 3). There was no significant difference between rates of complications in children who had surgery in the first time frame versus the second time frame (p = 0.7 and p = 0.8) (Supplemental Fig. 2). Lastly, there was no significant difference in 5-year PFS and OS (p = 0.6 and p > 0.99) and 10-year PFS and OS (p = 0.8 and p > 0.99) between children with severe complications and those without.

Long-Term Visual Status
Of the 83 children, information on preoperative visual status was available for 66 children. Seventeen children had unknown preoperative visual status or were unable to be evaluated due to age. Preoperative visual status was normal in 16 children (24%), impaired in 47 children (71%), and 3 children (5%) were blind at the time of diagnosis. Visual status at last follow-up was available in
65 children (Fig. 5). Although only 4 patients experienced severe visual deficit from surgery, at last follow-up, 15 children (23%) had worse vision and 5 (8%) became newly blind, with 36 children (55%) having stable vision and 9 (14%) having better vision.

**Discussion**

This surgical series spans an era in which radiation therapy was the primary treatment, through the development of more effective chemotherapies, and now at the introduction of molecular-based treatments. Part of the initial impetus of performing a resection was to delay the initiation of radiation therapy. Serendipitously, we noticed that a number of patients remained stable, leading us to adopt a philosophy of initial resection and avoid adjuvant therapy until progression. During this time, adjuvant and neoadjuvant medical therapy has proven to be efficacious leading to a redefinition of surgical goals and indications. We have attempted to define, based on this retrospective review, those indications for surgery as well as the patients in whom operative intervention should not be considered. It was evident midway through this experience that children younger than 2 years did not receive sufficient benefit from resection; thus, the last resection in a patient younger than 2 years in this series was performed in 2004. The indications for surgery may continue to change in the future as the chemotherapies evolve and molecular-based therapies prove efficacious, which will likely increase the indication for tissue retrieval for targeted therapy.

Among the difficulties in the management of OPG is deciding which treatment modality to use at various stages of the disease. The resection of exophytic chiasmatic/hypothalamic OPGs in children can lead to long-term PFS and OS in a subgroup of children, but it may be associated with a significant rate of complications, even in high-volume centers. The role of surgery as the primary treatment of OPGs continues to be controversial, although resection is often used as a second- or third-line treatment after chemotherapy. In the present series, there was no difference in either PFS or OS between patients treated first-line with surgery alone and those who had surgery as part of their second- or third-line treatment, with approximately half of the patients in both groups experiencing a benefit from resection.

Surgery for both primary and recurrent tumors can be efficacious, with nearly half of the children with OPG experiencing long-term or permanent remission. Interestingly, those patients in whom chemotherapy failed have a retrieval rate similar to those treated upfront with surgery. Resection at the time of failure of the primary treatment (chemotherapy and/or radiation therapy) may produce significant remission in and of itself in approximately half of the children. This role of surgery as secondary treatment after primary treatment failure is expected to diminish in the next few years with the increasing use of targeted therapy as second-line treatment after failed conventional chemotherapy and might well be used as first-line treatment in the future. The 5- and 10-year PFSs of exophytic hypothalamic/chiasmatic OPG with multiple treatment mo-

### TABLE 2. Complications after surgery in 83 patients

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of severe complications</td>
<td>13 (16)</td>
</tr>
<tr>
<td>New disabling visual deficit</td>
<td>4 (5)</td>
</tr>
<tr>
<td>New permanent focal neurological deficit</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Infection</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Incidence of nonsevere complications</td>
<td>16 (19)</td>
</tr>
<tr>
<td>New nondisabling visual deficit</td>
<td>3 (4)</td>
</tr>
<tr>
<td>New transient focal neurological deficit</td>
<td>14 (17)</td>
</tr>
<tr>
<td>New hormone deficit</td>
<td>18 (22)</td>
</tr>
</tbody>
</table>

### TABLE 3. Correlation of treatment and tumor characteristics with complications after surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe Complication</th>
<th>New Hormonal Deficit</th>
<th>New Permanent FND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at op</td>
<td>0.57</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>Extent of resection</td>
<td>0.63</td>
<td>0.42</td>
<td>0.25</td>
</tr>
<tr>
<td>Treatment prior to op</td>
<td>&gt;0.99</td>
<td>&gt;0.99</td>
<td>0.70</td>
</tr>
<tr>
<td>No hypothalamic involvement</td>
<td>0.31</td>
<td>0.65</td>
<td>0.48</td>
</tr>
<tr>
<td>Inferior location of tumor</td>
<td>0.50</td>
<td>0.78</td>
<td>0.17</td>
</tr>
<tr>
<td>Superior location of tumor</td>
<td>&gt;0.99</td>
<td>0.18</td>
<td>0.20</td>
</tr>
</tbody>
</table>

FND = focal neurological deficit.
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...dailities have been reported as 44%–68% and 46%–58%, respectively,\textsuperscript{1,14,25} which are comparable to the PFSs reported in this series (55% 5-year PFS and 46% 10-year PFS). OS decreased in our series from 87% at 5 years to 78% at 10 years. This is similar to the findings of Khafaga et al., who reported significant mortality over time of posterior OPG tumors with a 5-year OS of 88% declining to 46% by 10 years.\textsuperscript{14} In the COG (Children’s Oncology Group) trial reported by Ater et al., despite early progression, the 5-year OS of hypothalamic/chiasmatic was around 87%.\textsuperscript{1} Our 5-year PFS and OS (55% and 87%, respectively) are similar to those reported by Ater et al. The higher 10-year OS of 78% in the current series may reflect differences in the average age of our patients or technical factors, such as a favorable epicenter of the tumor or growth pattern that permitted our patients to undergo surgical intervention.

There is controversy about whether or not surgery should be used as first-line therapy because of the concern for complications after surgery that would not be seen with a noninvasive treatment. These complications include new hormonal deficits, loss of vision, and neurological deficit. Due to these risks, some believe that diffuse chiasmal involvement might be a contraindication to surgery.\textsuperscript{12} In our study, the most common complication was a new hormonal deficit in 18 children (22%); however, it must be noted that endocrine abnormalities are considered perhaps the most commonly seen sequelae of OPG and its treatment, and these might be due in large part to the tumors themselves and not merely the treatment.\textsuperscript{12} Thirteen children (16%) ultimately suffered a severe complication. Unfortunately, in this study, we could not identify which children are at a higher risk of complication and complications were not associated with the extent of resection, PFS, or OS.

It is known that most OPGs are diagnosed as a PA, a benign tumor that grows slowly. However, there are a number of patients that continue to have recurrences after multiple treatments. In 2007, the WHO officially recognized PMXA as a distinct variant of tumor.\textsuperscript{22} Since then, PMXAs have been considered to be more aggressive than PAs with lower OS and PFS when compared with PAs.\textsuperscript{16} In our study, we had a low number of PMXAs, with only 12 patients having either PMXA or a tumor with pilomyxoid features. The 5-year OS was shown to be statistically significantly worse in patients with PMXA or tumor with pilomyxoid features.

It has been previously reported that young age at presentation or treatment can have a worse prognosis with OPGs.\textsuperscript{27,30} This study confirms young age as a risk factor for worse OS. Since the adverse impact of younger age is seen in multiple studies of children with OPGs, including studies on the effect of chemotherapy,\textsuperscript{18,27} this may be an indication that tumors occurring in younger patients may in fact be more aggressive or less amenable to pharmacological or surgical treatment, or due to a combination of factors. This is further reported in recent literature showing that PMXAs tend to develop more commonly in younger patients.\textsuperscript{15,17} A prospective study looking at histology and outcomes in and targeted treatments for infants with OPG could be useful to better understand this process.

Visual impairment after treatment of an OPG can cause significant morbidity and lower competence in completing daily activities.\textsuperscript{2} A majority of pediatric patients with OPG experience long-term visual impairment.\textsuperscript{35} Of the 65 children in our study who had both preoperative and postoperative visual evaluations, 69% had stable or improved vision at last follow-up. Stable or improved vision after chemotherapy has been reported in 59%–72% of patients with neurofibromatosis type 1 (NF1) and 61% in sporadic cases, which is consistent with what we saw in our cohort.\textsuperscript{6,7} Furthermore, all patients in our study had chiasmatic/hypothalamic involvement of their tumor, which is known to be a poor prognostic factor for visual outcome.\textsuperscript{5} Additionally, children with sporadic OPGs, which constituted 90% of our cohort, tend to have worse visual outcomes than NF1 patients.

Although surgery is efficacious and carries 10-year PFS that is similar to that of chemotherapy in older children, the evolution of new chemotherapies, including molecular-based BRAF and MEK inhibitors, may demonstrate better side-effect profiles and relegate surgery to a second-line treatment.\textsuperscript{32,34} This would definitely be the situation at the
present time in children younger than 2 years and may ultimately be preferable in the vast majority of newly diagnosed patients. The early results from exploratory studies are promising; however, the durability of treatment, complete side-effect and complication profile, and long-term impact remain unknown. Despite the complications inherent to surgery, it may be the most efficacious treatment for select patients, especially if the child presents with increased intracranial pressure from tumor mass, hydrocephalus from a resectable third ventricle tumor, or extrinsic compression of the visual apparatus, or if progression under chemotherapy is detected. The risk of complications highlights that the decision for surgery should be made in collaboration with the family and an interdisciplinary treatment team.

A limitation of this study is the retrospective method and the inherent bias of including only children who were referred and amenable to surgical intervention. While our study was able to show that pretreatment did not significantly influence the outcomes of surgical candidates, we did not compare our surgical outcomes with those of biopsy and/or chemotherapy alone and those of patients who did not require surgery or were not surgical candidates. Although our 5-year PFS after primary surgery was similar to that experienced with chemotherapy, we were not able to demonstrate what factors predict which children will experience prolonged PFS after primary surgical intervention without additional adjuvant therapy and would therefore be the ideal surgical candidates.

Conclusions

This historical series represents the evolution of treatment of OPGs over the course of 3 decades. This experience has demonstrated that surgery is an efficacious treatment option, especially in children 2 years or older, but it does carry a significant risk of complications. Current treatment paradigms favor chemotherapy as the initial therapy for all children younger than 2 years and many 2 years or older. In this series, we have seen that there is a subset of children who can be treated with surgery alone and experience durable long-term disease control, but we are unable to specify which children, other than those 2 years or older and those with a histological diagnosis of a PA, would benefit. Considering the risks associated with surgery, an interdisciplinary approach should be used to assess the best treatment option for each child. For children who have tumor progression while being treated with chemotherapy, we believe that resection has a beneficial role both as a stand-alone treatment and as part of further multimodality therapies. More translational research is necessary to delineate the effects of age and histology of the tumor on progression and survival, especially considering the new entity of PMXAs.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Supplemental Information
Online-Only Content
Supplemental material is available with the online version of the article.


Previous Presentations
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