Pediatric Pleomorphic Xanthoastrocytoma: A National Database Inquiry on Current Treatment Approaches in the United States

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Abstract

**Background:** Pleomorphic xanthoastrocytomas (PXAs) account for <1% of primary brain tumors, occurring predominantly in children and young adults. Surgical resection serves as the primary treatment for PXAs, while radiotherapy (RT) and chemotherapy protocols remain poorly defined.

**Aim:** This study aims to determine current care patterns utilized for pediatric patients (≤18 years) diagnosed with PXAs and their effect on overall survival.

**Methods:** The United States National Cancer Database (NCDB) was queried between 2004 and 2015 for pediatric patients (≤18 years) diagnosed with PXAs.

**Results:** From the 224 qualifying patients, most patients proceeded with surgery only (78.1%), while 11.6% of patients received both adjuvant RT and chemotherapy. In the 2010-2015 cohort, patients with subtotal resection were associated with poorer prognosis than those with gross-total resection (hazard ratio = 17.44, 95% confidence interval = 2.10-144.90, p < .001). RT and chemotherapy recipients were similarly associated with poorer survival than those treated with surgery only, with p-values of <.001 and respective hazard ratios of 3.82 (95% confidence interval = 1.85-7.90) and 6.68 (95% confidence interval = 3.21-13.89). The key factors impacting the probability of RT delivery involved WHO grade (p < .001) and chemotherapy administration (p < .001). However, WHO grade alone did not significantly impact survival (p-value = .088).

**Conclusion:** Maximally safe resection is the current treatment goal for patients with PXAs. RT and chemotherapy are poorly utilized but had a greater role in managing more aggressive cases of PXAs. Additional research focusing on the impact of adjuvant therapies on tumor progression is needed to better guide treatment decisions.

**KEYWORDS**
anaplastic pleomorphic xanthoastrocytoma, National Cancer Database, overall survival, pediatric, pleomorphic xanthoastrocytoma, radiotherapy
1 | INTRODUCTION

Pleomorphic xanthoastrocytomas (PXAs) are rare neuroglial tumors that occur predominantly in children and young adults. They account for <1% of primary brain tumors and are considered World Health Organization (WHO) grade II tumors. They are associated with favorable prognosis with respective 5-year and 10-year overall survival (OS) rates of about 77.8% and 68.5%, with an approximate 5-year progression-free survival (PFS) rate of 68.3%. However, these tumors may transform into anaplastic PXAs in 15%-20% of patients. aPXAs are defined as a subset of PXAs in the revised 2016 WHO classification for central nervous system (CNS) tumors. These tumors are considered WHO grade III with their increased mitotic activity of ≥5 per high-powered fields. They present with a higher likelihood for necrosis, proliferation, absent pericellular reticulin, and infiltration.

Complete surgical resection presently serves as the primary treatment for PXAs, while the role of adjuvant radiotherapy (RT) and chemotherapy in managing this disease remains undefined. To gain a better understanding of care patterns for pediatric PXAs, the current study aims to evaluate the effect of treatment, particularly RT, on OS using the United States National Cancer Database (NCDB).

2 | METHODS

The NCDB was established in 1988 by the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. It is a hospital-based cancer registry that collects information on patients receiving care from a CoC-accredited institution, which comprises 30% of 5000+ hospitals in the United States. Information reported in the NCDB include deidentified sociodemographic, treatment, tumor, and survival data of oncology patients.

Based on the International Classification of Diseases for Oncology, 3rd edition Histology code of 9424/3, a search through the United States National Cancer Database (NCDB) was conducted for pediatric patients (≤18 years) diagnosed with PXAs in 2004-2015. The data were exported on February 28, 2020, by authors Y.Y., C.B., and Y.C. These authors verified the data to ensure no problem occurred while data export. Descriptive analysis was conducted summarizing patient demographic and clinical characteristics. To increase transparency concerning the impact of patients with missing values in the study analyses, footnotes referring to the inclusion or exclusion of these patients were provided for each table.

Patients were categorized in two treatment groups: “surgery only” and “surgery and RT.” To assess for differences in patient characteristics between treatment groups, Kruskal-Wallis test was used for continuous variables (i.e., age and tumor size); Cochran-Armitage test was used for three-level ordinal variables (i.e., comorbidity score); and Fisher’s exact test was used for other categorical variables. Analyses concerning extent of resection (EOR) were based on patients diagnosed between 2010 and 2015 as such information was made available in the database. Our variables were analyzed utilizing log rank testing and Kaplan-Meier modeling. OS was defined as the time in months from diagnosis to death or last follow-up, whichever occurs first. Univariate and multivariable Cox proportional hazard ratio models were fitted to the data. The final multivariable model was determined based on purposeful selection combined with Akaike’s information criterion and Bayesian information criterion. All analyses were performed using R-version 3.6.2. p-values of <.05 were considered statistically significant. Data consisting of <20 patients were deidentified with asterisks (*) and reported only in percentages.

3 | RESULTS

For the 224 eligible, pediatric patients, an almost equal occurrence was found between males and females with a median diagnosis age of 14 years (Table 1). Most patients identified as Caucasian (63.8%), followed by Black (16.1%) and Hispanic patients (14.7%). Many residents in a region where ≥14% of adults had no high school degree (60.3%) and earned a median income of <$46,000 (63.8%). Most lived in a metropolitan area (62.1%) and had private insurance (62.5%). Almost an equal number of patients were observed in 2004-2009 and 2010-2015, with many presenting without comorbidities (90.2%). The tumor primarily occurred at the temporal lobe (34.4%) and had a median tumor size of 40 mm (range = 5-988 mm). The WHO grades were predominantly unspecified (68.8%), but WHO grade IV tumors and PXAs (i.e., WHO grade II), respectively, comprised of 12.9% and 11.6%. A limited number of patients were biopsied (8.0%). Most patients underwent surgery (97.3%). Of the 222 patients with known RT delivery, 18.8% received RT at a median dose of 54.0 Gy (range = 5.4-83.4 Gy). The preferred RT modality was intensity-modulated RT (35.7%), followed by photon therapy (31.0%). Chemotherapy was administered to 14.7% of patients.

Patients who underwent surgery and had complete RT information comprised of 216 patients, of which 81.0% had surgery only (Table 2). Based on the Fisher’s exact tests, factors significantly associated with RT delivery included: WHO grade (P < 0.001) and chemotherapy administration (P < .001). Most, if not all, PXAs with WHO grades I, II, and III were typically resected without RT (100%, 96%, and 55.6%, respectively), while more WHO grade IV tumors underwent RT postsurgery (55.6%). Those receiving chemotherapy more likely received surgery with RT (83.9%).

The median OS time of the entire cohort was indeterminate due to the limited number of events (i.e., deaths) observed. However, 3- and 5-year OS rates were calculated for selected groups of subjects (Table 3). The 3-year OS for patients, respectively, without and with RT were 94.4% (95% confidence interval [CI] = 89.2%-97.4%) and 65.2% (95% CI = 46.7%-78.7%). Based on the log rank test and Kaplan-Meier curves, OS is significantly longer for non-RT compared to RT recipients (P < .001, Table 4, Figure 1). Adjuvant chemotherapy administration also affected OS (P < .001, Table 4), with higher 3-year OS for nonchemotherapy (94.8%, 95% CI = 89.9%-97.4%) versus chemotherapy recipients (51.4%, 95% CI = 30.1%-69.1%).
The 2010-2015 cohort \((n = 103)\) indicated that most had gross-total resection \((\text{GTR}, 64.9\%)\) rather than subtotal resection \((\text{STR})\) (Table 1). With only 79.6\% of the 2010-2015 cohort having known survival outcomes, the log rank test revealed GTR impacted survival \((p < .001, \text{Table 4})\). Increased OS was observed in patients who underwent GTR rather than STR \((3\text{-year OS} = 97.5\%, 95\% \text{CI} = 83.5\%-99.6\% \text{vs.} \ 73.7\%, 95\% \text{CI} = 47.6\%-88.2\%, \text{Table 3})\).

### TABLE 1

Overall characteristics of pediatric pleomorphic xanthoastrocytomas \((N = 224)\)

| Variable                                      | \(N\) (\%) |
|-----------------------------------------------|------------|
| **Age (years, \(N = 224)\)**                 |            |
| Median (range)                                | 14 (1-18)  |
| **Sex \((N = 224)\)**                        |            |
| Male                                          | 115 (51.3\%)|
| Female                                        | 109 (48.7\%)|
| **Race \((N = 224)\)**                       |            |
| Caucasian                                     | 143 (63.8\%)|
| Black                                         | 36 (16.1\%) |
| Hispanic                                      | 33 (14.7\%) |
| Other                                         | (5.4\%)    |
| **Median income \((N = 215)\)**              |            |
| \(< \$46\ 000\)                               | 143 (63.8\%)|
| \(\geq \$46\ 000\)                           | 72 (32.1\%) |
| (Missing)                                     | (4.0\%)    |
| **% without high school degrees \((N = 215)\)**|            |
| \(\geq 14\%\)                                 | 135 (60.3\%)|
| \(< 14\%\)                                   | 80 (35.7\%) |
| (Missing)                                     | (4.0\%)    |
| **County population \((N = 215)\)**          |            |
| Metropolitan, \(>250\ 000\)                   | 139 (62.1\%)|
| Nonmetropolitan                               | 76 (33.9\%) |
| (Missing)                                     | (4.0\%)    |
| **Insurance status \((N = 215)\)**           |            |
| Private                                       | 140 (62.5\%)|
| Government                                    | 68 (30.4\%) |
| None                                          | (3.1\%)    |
| (Missing)                                     | (4.0\%)    |
| **Year of diagnosis \((N = 224)\)**          |            |
| 2004–2009                                     | 113 (50.4\%)|
| 2010–2015                                     | 111 (49.6\%)|
| **Comorbidities \((N = 224)\)**              |            |
| 0                                             | 202 (90.2\%)|
| 1                                             | (6.7\%)    |
| \(\geq 2\)                                    | (3.1\%)    |
| **Tumor location \((N = 224)\)**             |            |
| Temporal lobe                                 | 77 (34.4\%) |
| Frontal lobe                                  | 46 (20.5\%) |
| Overlapping lesion of brain                   | 29 (12.9\%) |
| Others                                        | 27 (12.1\%) |
| Parietal lobe                                 | 25 (11.2\%) |
| Occipital lobe                                | (8.9\%)    |
| **Tumor size (mm, \(N = 161\))**             |            |
| Median (range)                                | 40 (5–988) |
| **WHO Grade \((N = 224)\)**                  |            |
| NOS                                           | 154 (68.8\%)|

(Continues)

### TABLE 1 (Continued)

| Variable                                      | \(N\) (\%) |
|-----------------------------------------------|------------|
| **Biopsy \((N = 222)\)**                     |            |
| None                                          | 203 (90.6\%)|
| Biopsy, primary site                          | (8.0\%)    |
| Surgical procedure with a bypass, no biopsy   | (0.4\%)    |
| (Missing)                                     | (0.9\%)    |
| **Surgery \((N = 224)\)**                    |            |
| Yes                                           | 218 (97.3\%)|
| No                                            | (2.7\%)    |
| **Extent of Surgery (2010–2015 data, \(N = 103\))** |            |
| GTR                                           | 72 (64.9\%) |
| STR                                           | 31 (27.9\%) |
| (Missing)                                     | (7.2\%)    |
| **RT \((N = 222)\)**                         |            |
| No                                            | 180 (80.4\%)|
| Yes                                           | 42 (18.8\%) |
| (Missing)                                     | (0.9\%)    |
| **RT Dose (GY, \(N = 37\))**                 |            |
| Median (range)                                | 54 (5.4–83.4) |
| **RT Modality \((N = 42)\)**                 |            |
| Intensity-modulated RT                        | (35.7\%)   |
| Photons                                       | (31.0\%)   |
| External beam, NOS                            | (19.0\%)   |
| Conformal or 3-D therapy                      | (7.1\%)    |
| Stereotactic radiosurgery, NOS                | (2.4\%)    |
| Gamma Knife                                   | (2.4\%)    |
| Other, NOS                                     | (2.4\%)    |
| (Missing)                                     | (0.05\%)   |
| **Chemotherapy \((N = 222)\)**                |            |
| No                                            | 189 (85.1\%)|
| Yes                                           | 33 (14.7\%) |
| (Missing)                                     | (0.9\%)    |

Abbreviations: GTR, Gross total resection; NOS, not otherwise specified; RT, radiotherapy; STR, subtotal resection.

*Patient populations with <20 patients were reported with asterisks (*) for de-identification purposes.

*Patients with missing values were included in analyses.

The 2010-2015 cohort \((n = 103)\) indicated that most had gross-total resection \((\text{GTR}, 64.9\%)\) rather than subtotal resection \((\text{STR})\) (Table 1). With only 79.6\% of the 2010-2015 cohort having known survival outcomes, the log rank test revealed GTR impacted survival \((p < .001, \text{Table 4})\). Increased OS was observed in patients who underwent GTR rather than STR \((3\text{-year OS} = 97.5\%, 95\% \text{CI} = 83.5\%-99.6\% \text{vs.} \ 73.7\%, 95\% \text{CI} = 47.6\%-88.2\%, \text{Table 3})\). EOR and
TABLE 2  Key variables associated with surgery ± Radiotherapy in pediatric pleomorphic xanthoastrocytomas (N = 216)

| WHO grade | Surgery N (Row %) | Surgery + RT N (Row %) | p-value |
|-----------|------------------|------------------------|---------|
| I         | 175 (81.0%)      | 41 (19.0%)             | <.001   |
| II        | (100%)           | (0.0%)                 |         |
| III       | 24 (96%)         | (4%)                   |         |
| IV        | (55.6%)          | (44.4%)                |         |
| NOS       | 128 (85.9%)      | 21 (14.1%)             |         |

| Chemotherapy | Surgery N (Row %) | Surgery + RT N (Row %) | p-value |
|--------------|------------------|------------------------|---------|
| No           | 169 (91.8%)      | 26 (83.9%)             | <.001   |
| Yes          | (16.1%)          | (100%)                 |         |
| (Missing)    | (100%)           | (0 %)                  |         |

Abbreviations: NOS, Not otherwise specified; RT, radiotherapy.

Patient populations with <20 patients were reported with asterisks (*) for de-identification purposes.

Patients with missing values were excluded from analyses (N = 8).

chemotherapy also affected survival (p < .001, Table 4). Whereas minor differences in the 3-year OS were observed in patients having GTR with or without chemotherapy, a major difference in 3-year OS was seen for patients having STR with and without chemotherapy (3-year OS = 40%, 95%CI = 5.2%-75.3% vs. 85.1%, 95% CI = 52.3%-96.1%, respectively). Although there were too few patients to make the log rank test reliable, similar results were observed for those receiving surgery with or without RT (p < .001, Table 4). There was little difference in 3-year OS for patients having GTR with and without adjuvant RT, but increased 3-year survival was observed in patients undergoing only STR compared to patients proceeding with adjuvant RT (3-year OS = 93.3%, 95% CI = 61.3%-99.0% vs. 33.3%, 95% CI = 4.6%-67.6%).

Univariate cox regression analyses indicated EOR (p < .001) and the administration of RT (p < .001) and chemotherapy (p < .001) independently affect OS (Table 5). STR patients had a higher mortality risk (hazard ratio [HR] = 17.44, 95% CI = 2.10-144.90) relative to GTR patients. Compared to patients without adjuvant therapies, RT and chemotherapy recipients respectively had HRs of 3.82 (95% CI = 1.85-7.90) and 6.68 (95% CI = 3.21-13.89). Only receipt of chemotherapy remained significant in the multivariable model.

4  | DISCUSSION

PXAs were first detailed by Kepes et al in 1979.4,5,12 However, due to the infrequent occurrence of this disease, current literature concerning PXAs comprise primarily of case reports and scarce case series.3,5 The publication on PXAs by Perkins et al3 (n = 215) resembles the present study, as it examined the effects of demographic, clinical, and treatment variables on OS for patients with PXAs. Perkins et al queried the Surveillance, Epidemiology, and End Results cancer registry for children and adults diagnosed with PXAs between 1981 and 2007. Relative to Perkins et al, the present study contains twice the number of pediatric patients. The present study’s focus on children over the past 12-years also limited the effect of temporal bias, as it confined diagnostic and treatment variation on a multi-institutional level.

Even though Perkins et al3 included both children and adults in their study, they similarly observed that most patients identified as Caucasian (80%). Their data also indicated that race did not impact survival (p = .40). Our analyses further indicated likelihood of RT delivery and mortality risk were not significantly associated with patient demographics. RT delivery was more impacted by WHO grade and chemotherapy delivery, while significant mortality risk was associated with EOR and administration of RT and chemotherapy.

Histologically, PXAs are characterized by astrocytes that usually have large mono- or polynucleated structures and spindle cells with a mesenchymal appearance oriented in intersecting bundles.1,6 They are distinguishably pleomorphic with some containing lipid droplets. They typically have granular bodies differing in texture, size, and eosinophilia, in addition to the rare observation of some mitotic activity and a general lack of necrosis.5,6,8 aPXAs have an increased mitotic activity, which is observed as necrosis and hypercellularity.5 Presently, aPXAs are only diagnosed based on histopathologic findings, and the mechanisms that result in its malignancy are unknown.9 In the present study, only 8.0% of patients in the overall cohort underwent biopsy, but 4.0% and 12.9% were respectively classified as aPXAs and WHO grade IV tumors. The discrepancy between the number of biopsied patients and reported high-grade PXAs raises concerns regarding the putative diagnosis of PXAs in the NCDB, as the current standard practice of diagnosing high-grade PXAs requires histological confirmation.

PXAs are strictly defined as WHO grade II (i.e., PXAs) and WHO grade III (i.e., aPXAs) tumors, according to the 2016 WHO classification for CNS tumors. However, cancer databases include WHO grade I and IV tumors in PXA cohorts. When considering the occurrence of PXA in all WHO grades, Perkins et al7 reported the highest frequency of PXAs (19%), followed by aPXAs (12%), WHO grade IV lesions (11%), and WHO grade I tumors (4%). Most PXAs (54%) noted by Perkins et al,3 however, had unknown WHO grades. By contrast, the present study contained a higher rate of WHO grade IV tumors (12.9%), followed by PXAs (11.6%), aPXAs (4.0%), and WHO grade I lesions (2.7%). Nonetheless, like Perkins et al, the present study observed most tumors having unknown WHO grades (68.8%). The rationale behind the diagnosis of PXAs as WHO grade I and IV tumors in cancer databases warrant evaluation in order to determine the appropriateness of these tumor grades, as these tumor grades fall outside the present WHO classification system for PXAs.

PXAs may be erroneously diagnosed as glioblastomas (GBMs).8,13-15 GBMs are commonly mistaken for aPXAs, as they appear similar in radiographic images and exhibit high mitotic activity and frequent necrosis.16,17 The absence of appropriate nuclear pleomorphism, abundant reticulin sites, lymphocytic infiltration, and lipid-filled cytoplasmatic are also associated with aPXAs and a variety of GBMs.16,18 By contrast, patients with PXA WHO grade IV tumors
TABLE 3 Summary of overall survival rates of pediatric pleomorphic xanthoastrocytomas

| Variable | N   | 3-year OS % (95% CI) | 5-year OS % (95% CI) |
|----------|-----|----------------------|----------------------|
| **Extent of Surgery**<sup>a,c</sup> (N = 82) |
| GTR      | 60  | 97.5 (83.5-99.6)     | 97.5 (83.5-99.6)     |
| STR      | 22  | 73.7 (47.6-88.2)     | 61.5 (29.4-82.4)     |
| **Extent of Surgery + Chemotherapy**<sup>a,c</sup> (N = 82) |
| GTR      | 56  | 97.3 (82.3-99.6)     | 97.3 (82.3-99.6)     |
| GTR + Chemotherapy | a∗ | 100 (N/A)       | N/A                  |
| STR      | a∗  | 85.1 (52.3-96.1)     | 70.9 (30.9-90.4)     |
| STR + Chemotherapy | a∗ | 40 (5.2-75.3)     | N/A                  |
| **Extent of Surgery + RT**<sup>a,c</sup> (N = 81) |
| GTR      | 50  | 97 (80.4-99.6)       | 97 (80.4-99.6)       |
| GTR + RT | a∗  | 100 (N/A)          | N/A                  |
| STR      | a∗  | 93.3 (61.3-99.0)     | 77.8 (31.6-94.7)     |
| STR + RT | a∗ | 33.3 (4.6-76.7)     | N/A                  |
| **RT**<sup>c</sup> (N = 199) |
| No       | 161 | 94.4 (89.2-97.2)     | 88.4 (81.0-93.1)     |
| Yes      | 38  | 65.2 (46.7-78.7)     | 60.9 (41.7-75.5)     |
| **Chemotherapy**<sup>c</sup> (N = 199) |
| No       | 171 | 94.8 (89.9-97.4)     | 89.2 (82.2-93.5)     |
| Yes      | 28  | 51.4 (30.1-69.1)     | 45 (23.6-64.2)       |
| **Race**<sup>c</sup> (N = 201) |
| Caucasian| 127 | 87.5 (79.7-92.4)     | 82.5 (73.4-88.7)     |
| Black    | 31  | 96.7 (78.6-99.5)     | 92.1 (71.3-98.0)     |
| Hispanic | 32  | 92.6 (73.5-98.1)     | 81.7 (57.1-93.0)     |
| Other    | a∗  | 70.1 (32.3-89.5)     | 70.1 (32.3-89.5)     |
| **WHO Grade**<sup>c</sup> (N = 201) |
| I        | a∗  | 100 (N/A)           | 100 (N/A)            |
| II       | 22  | 95.2 (70.7-99.3)     | 89.3 (63.2-97.2)     |
| III      | a∗  | 75 (31.5-93.1)       | 60 (19.5-85.2)       |
| IV       | 24  | 70.3 (44.7-85.7)     | 70.3 (44.7-85.7)     |
| NOS      | 143 | 91.2 (84.7-95.1)     | 85.5 (77.1-91.0)     |

Abbreviations: CI, Confidence interval; GTR, gross total resection; N/A, not available; NOS, not otherwise specified; OS, overall survival; RT, radiotherapy; STR, subtotal resection.

<sup>a</sup>Patient populations with <20 patients were reported with asterisks (*) for de-identification purposes.

<sup>b</sup>The findings reported are based on the 2010-2015 data only.

<sup>c</sup>Patients with missing values were excluded from analyses.

Exhibit longer median OS than patients with GBMs (3.75 years vs. 6 months, p < .0001).<sup>3</sup> BRAF V600E mutations typically do not occur in GBM cases, whereas one study observed such mutations were more prominent in PXAs and aPXAs in relation to other CNS tumors in adults and children.<sup>7,19</sup> The presence of such mutations may serve as a useful marker to differentiate PXAs from GBM but warrant further investigation.<sup>19</sup> Due to the challenges of differentiating between PXAs and GBMs, some PXAs may be misdiagnosed as GBMs and vice versa. This may also explain the consideration of some PXAs as WHO grade IV tumors in the NCDB.

BRAF V600E mutations were reported to occur in 65% and 78% of PXAs.<sup>2,8,9,19</sup> These mutations also appear to occur at an equal rate between PXAs and aPXAs.<sup>9,19</sup> In a study’s PXA cohort (N = 87), Schindler et al<sup>19</sup> observed that these mutations appeared more prevalent in children with aPXAs (100%) than in adults with aPXAs (38%). These mutations arguably may serve as a reasonable diagnostic marker for aPXAs. The presence of BRAF V600E mutations was associated with increased OS in relation to BRAF V600E nonmutant tumors in general PXA cases (p = .02).<sup>2</sup> However, Schindler et al postulated that such an increased survival may be due to a higher frequency of BRAF V600E mutations in PXAs (75.0%) rather than aPXAs (47.4%). Multivariable analysis based on WHO grade and presence of these mutations were encumbered by the small number of events in the study series.

Tone et al<sup>20</sup> found that out of 27 patients, 48% of patients with either PXAs or aPXAs expressed the BRAF V600E mutation.
Several studies have noted that EOR affects patient outcomes. Perkins et al. observed that 68% of PXA patients had GTR, while 22% had either debulking or partial resection. The latter group were not significantly associated with survival outcomes in univariate analyses (HR = 1.48, 95% CI = 0.82-2.7, p = .19) or multivariable analyses (HR = 1.26, 95% CI = 0.69-2.30, p = .45). Similar HRs were seen by Mallick et al. However, Mallick et al. noted significant differences in OS between patients with GTR and STR in univariate and multivariable cox regression analyses with respective p-values of .017 and .005. The present study did not observe a significant difference in survival between patients with and without surgical resection (p = .533). This finding may have been affected by the low number of patients that did not undergo resection.

Although the NCDB only provided information on EOR from 2010 to 2015, the current study observed that 69.9% of patients with known EOR underwent GTR, while the remaining 30.1% underwent STR. Like prior studies, EOR was shown to impact survival (p < .001, log-rank test; p < .001, univariate cox regression). Patients with STR were associated with decreased survival compared with GTR (HR = 17.44, 95% CI = 2.10-144.90). Similarly, reduced 3-year OS was observed in patients proceeding with STR versus GTR (3-year OS = 92.1%, 95% CI = 87.6-96.6% vs. 68.5%, 95% CI = 62.1-74.9%).

Perkins et al. noted RT was administered in 25% of the study cohort. Increased mortality risk was observed in RT versus non-RT recipients in univariate analyses (HR = 4.47, 95% CI = 2.61-7.66, p < .0001) and multivariable analyses (HR = 3.66, 95% CI = 2.06-6.41, p < .0001). In this study, multivariable analyses were adjusted for statistically significant variables in the univariate analyses with p < .10 level (e.g., surgery, RT, age and sex). The study suspected the increased risk in patients undergoing RT may be attributed to most RT

**TABLE 4** Key variables determined via log rank test for pediatric pleomorphic xanthoastrocytomas

| Variables                           | N   | p-value |
|-------------------------------------|-----|---------|
| GTR versus STR<sup>b</sup>          | 82  | <.001   |
| Extent of Surgery + Chemotherapy<sup>ab</sup> | 81  | <.001   |
| Extent of Surgery + RT<sup>ab</sup>  | 81  | Not reliable |
| ± Adjunct RT<sup>b</sup>            | 199 | <.001   |
| ± Adjunct Chemotherapy<sup>b</sup>  | 199 | <.001   |
| Race<sup>b</sup>                    | 201 | .175    |
| WHO Grade<sup>b</sup>               | 201 | .088    |

Abbreviations: GTR, Gross total resection; RT, radiotherapy; STR, subtotal resection.

<sup>a</sup>The findings reported are based on the 2010-2015 data only.

<sup>b</sup>Patients with missing values were excluded from analyses.
patients having high-grade tumors (51%). Ida et al.² found that 47.3% of patients within their study received some form of postoperative therapy. They similarly observed that adjuvant therapies were more common in patients with aggressive tumors, which they classified based on patients experiencing an early event (i.e., recurrence or death within 3 years from initial diagnosis). RT administration was provided to 57.1% of patients with early events as opposed to 17.1% without early events ($P = 0.003$). Chemotherapy was delivered in 61.9% of patients with early events as opposed to 22.39% without ($p = 0.005$). Most patients who experienced an early event typically underwent STR/Biopsy, had tumors with a mitotic index of ≥5/10 HPF, and were diagnosed with aPXAs ($p = 0.004$, $p = 0.02$, and $p = 0.008$, respectively).

In the present study, RT and chemotherapy were administered in 18.8% and 14.7% of patients, respectively. Like Perkins et al.,³ RT recipients exhibited increased mortality risk over those without RT in our univariate analysis (HR = 3.82, 95% CI = 1.85-7.9, $p < .001$). Patients who received chemotherapy had increased mortality risk compared to those who did not receive chemotherapy ($p$-value $< .001$, log-rank test; HR = 6.68; 95% CI = 3.21-13.89, $p$-value $< .001$, univariate cox regression). Chemotherapy was commonly administered to RT recipients (63.4%, $p < .001$). WHO grade was frequently associated with RT administration ($p < .001$). WHO grade IV tumors likely received postoperative RT, while PXAs primarily underwent surgery only. These findings suggest that poor patient outcomes may be more attributed to the aggressive nature of high-grade tumors.  

### Table 5

| Variable          | N     | % of Events | HR (95% CI)         | $p$-value |
|-------------------|-------|-------------|---------------------|-----------|
| Sex $^U$ (N = 201) |       |             |                     | .229      |
| Male              | 104   | 10.6%       | Reference           |           |
| Female            | 97    | 19.6%       | 1.57 (0.75-3.31)    |           |
| Race $^U$ (N = 201) |     |             |                     | .175      |
| Caucasian         | 127   | 15.0%       | Reference           |           |
| Black             | 31    | 6.5%        | 0.4 (0.09-1.73)     |           |
| Hispanic          | 32    | 18.8%       | 1.46 (0.58-3.67)    |           |
| Other             | 11    | 27.3%       | 2.4 (0.71-8.14)     |           |
| WHO grade $^U$ (N = 201) |       |             |                     | .088      |
| I                 | a*    | 0%          | 0 (0-Inf)           |           |
| II                | 22    | 9.1%        | Reference           |           |
| III               | a*    | 37.5%       | 4.57 (0.76-27.40)   |           |
| IV                | 24    | 25%         | 3.81 (0.77-18.96)   |           |
| NOS               | 143   | 13.3%       | 1.57 (0.37-7.75)    |           |
| Surgery $^U$ (N = 201) |       |             |                     | .533      |
| No                | a*    | 25%         | Reference           |           |
| Yes               | 197   | 14.7%       | 0.54 (0.07-3.95)    |           |
| Extent of surgery $^U$ (N = 82) |        |             |                     | <.001     |
| GTR               | 60    | 1.7%        | Reference           |           |
| STR               | 22    | 27.3%       | 17.44 (2.10-144.90) |           |
| (Missing)         |       |             | N/A                 |           |
| RT $^U$ (N = 199) |       |             |                     | <.001     |
| No                | 161   | 10.6%       | Reference           |           |
| Yes               | 38    | 34.2%       | 3.82 (1.85-7.90)    |           |
| (Missing)         |       |             | N/A                 |           |
| Chemotherapy $^U$ (N = 199) |       |             |                     | <.001     |
| No                | 171   | 9.9%        | Reference           |           |
| Yes               | 28    | 46.4%       | 6.68 (3.21-13.89)   |           |
| (Missing)         |       |             | N/A                 |           |

Abbreviations: CI, Confidence interval; GTR, gross total resection; HR, hazard ratio; RT, radiotherapy; STR, subtotal resection; $^U$, Univariate; $^M$, Multivariable.

*aPatient populations with <20 patients were reported with asterisks (*) for de-identification purposes.

The findings reported are based on the 2010-2015 data only.

Patients with missing values were excluded from analyses.
rather than the administration of RT and chemotherapy, considering that such therapies were mostly utilized for WHO grade IV tumors in the study cohort.

Selection bias continues to be an issue in this study, since the cases in the NCDB are comprised of patients diagnosed and treated in facilities accredited by the Commission on Cancer. Additionally, although the NCDB comprises 72% of newly diagnosed cancer cases, the rarity of PXAs, the prevalence of missing information (e.g., EOR prior to 2009, WHO grade, and tumor size), and the poor utilization of adjuvant therapies limit the sample size and statistical power of the analyses. The NCDB reports on patients diagnosed outside of the WHO classification of PXAs, drawing concerns toward the misdiagnosis of WHO grade I and IV PXA cases. The potential for misdiagnosis is further increased by the limited information on the central review of pathology and molecular data in the NCDB. Vital statuses of patients diagnosed in 2015 could not be included in the 3- and 5-year survival analyses, censoring findings early in the data collection stage. Furthermore, since the NCDB contains information on newly diagnosed cancer cases, the impact of demographic, clinical, and treatment factors on PFS could not be evaluated. However, PFS remains a valuable outcome to evaluate in a condition that has a high tendency to recur.

Presently, maximally safe resection is the primary treatment recommendation for PXAs. Observation for younger patients who undergo GTR is a reasonable approach, as EOR and young age are considered significant factors in improved PFS and OS. Surveillance MRIs of the brain with contrast-enhancement is recommended at 3-month intervals during the first 3 years from diagnosis, biannually the following 2 years, and annually thereafter. If the tumor recurs, patients should pursue aggressive treatment, such as secondary surgery and RT. For tumors with atypical features, administering postoperative therapy, such as RT and chemotherapy, may be beneficial considering these tumors are associated with reduced survival and a higher likelihood for recurrence than PXAs.

5 | CONCLUSION

Maximally safe resection is the mainstay treatment for patients with PXAs. The role of adjuvant therapies, such as RT and chemotherapy, remains poorly defined but is greatly utilized post surgery for patients with high-risk disease. Further investigation is warranted to determine the use of adjuvant therapies in managing and minimizing tumor progression in PXAs.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.
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