## Title

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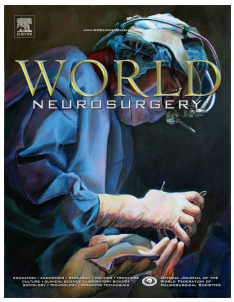


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# Pleomorphic Xanthoastrocytoma with anaplastic features: a retrospective case series

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**Abstract**

**Introduction:** Pleomorphic xanthoastrocytoma (PXA) is a unique meningocerebral glioma with relatively favorable prognosis. PXA also possess a variant with anaplastic features (aPXA) that is associated with poor outcomes. To date, few studies have examined the clinico-pathologic importance of these anaplastic features.

**Methods:** From 1999 to 2012, 8 patients with aPXA were treated at the University of California, San Francisco. Cases were re-confirmed by neuropathology, and clinical information regarding patient demographics, tumor characteristics, and treatment outcomes were assembled. Tumors were classified as aPXA according to the WHO diagnostic criteria established in 2007.

**Results:** There were 5 female and 3 male patients in our cohort, ranging in age from 4 to 74 years at initial diagnosis. Seizure was the most common presenting symptom (44%), and the majority of tumors arose in the frontal or temporal lobes (89%). Six patients received subtotal resection (STR), and all suffered from progression despite adjuvant radiotherapy and chemotherapy. Median time to progression was 20 months, with a 1 year progression-free survival rate of 57%. Three aPXA patients expired with a median survival of 87 months. Four patients developed disseminated disease. Three of 8 (38%) showed $BRAF^{v600}$ mutation.

**Conclusion:** aPXA is associated with poorer clinical outcomes compared to PXA. Gross total resection should be the goal of initial treatment. It remains unclear whether adjuvant radiation and chemotherapy are able to prevent progression or dissemination. Long-term monitoring of all patients is a critical step in management due to the potential for tumors to transform into higher grade lesions.

## Introduction

Pleomorphic xanthoastrocytoma (PXA) was first identified in 1979 by Kepes and colleagues as a unique meningocerebral astrocytoma with a relatively favorable prognosis despite its malignant pathologic features.[1] Composed of spindle cells and multi-nucleated giant cells, PXAs were also noted to contain large lipid droplets and abundant reticulin fibers that made them resemble fibrous xanthomas.[2] Subsequent immunohistochemical staining with glial fibrillary acidic protein made it possible to identify astrocytic components within the tumors and corroborated their standing as a unique neoplasm, with the World Health Organization (WHO) officially recognizing PXA as a distinct central nervous system (CNS) tumor in 1993.[3]

Though clinically indolent, PXA can undergo transformation into a true malignant glioma,[4] with progression rates between 10-38% occurring as late as 15 years after initial diagnosis.[4,5] This observation has underscored the importance of primary therapeutic interventions that minimize tumor recurrence and maximize overall survival (OS). Extent of resection (EOR) has been identified as an important determinant of OS,[6-9] while the utility of adjuvant radiation remains unclear, with most published accounts consisting of case reports.[10-12] Kepes *et al.* initially speculated that tumor features such as lack of necrosis, cystic composition, superficial cortical anatomy, and lymphocytic infiltrate were responsible for the favorable prognosis,[1] and a number of subsequent studies have largely validated this hypothesis, including a series of 71 patients in which OS rates were 81% at 5 years and 70% at 10 years.[7]

In 2007, the WHO re-classified PXA as a grade II tumor that can also be found "with anaplastic features" (aPXA).[13] These latter cases demonstrate variable levels of necrosis and/or ≥5 mitoses per high power field (hpf). These features are not only important diagnostic criteria, but also appear to hold prognostic value: mitotic index was found to be independently associated

with survival outcomes,[7] while necrosis appeared to be significantly associated with earlier mortality in one series[6] but not in another.[7] Nevertheless, PXA and aPXA are both regarded as grade II neoplasms despite little understanding of the impact of their pathological differences on clinical outcomes.

With few exceptions, aPXA has not been studied as an independent entity. In an effort to improve understanding of how pathological features influence outcomes for aPXA, we present our institutional experience in the management of 8 aPXA patients seen at the University of California, San Francisco (UCSF) from 1999-2012.

## Methods

### *Patient Population and Data Collection*

All consenting patients evaluated by the Department of Neurological Surgery at UCSF have had their names and pathological diagnoses collected and recorded in an IRB-approved program since 1991 (Committee for Human Research [CHR]# H7828-29842-01). We obtained further permission to study patients with aPXA (CHR# H41995-35010-01).

Patient records were reviewed to extract data on demographics, presentation and symptomatology, histopathologic features, treatment modality, morbidity and mortality, and follow-up. Extent of resection was determined based on review of pre- and post-operative scans, or through review of radiographic and clinic follow-up information if original scans were not available for review. Mortality data was confirmed using the social security death index, and all cases of recurrence and intracranial dissemination were documented radiographically. Length of progression-free survival (PFS) was defined as the time between initial treatment for aPXA and the most recent imaging study demonstrating radiographic absence or recurrence of tumor.

Length of OS was defined as the time between initial confirmatory diagnosis of aPXA and date of death or last known date of follow-up.

All patient information was compiled into a single Microsoft® Excel database. Patient data was analyzed by gender, age, race, length of survival, and mortality. Tumor data was analyzed by size, location, recurrence, metastasis, and pathological features including mitotic index and necrosis. Treatment data was analyzed by modality including EOR, use of adjuvant radiotherapy, use of Gamma Knife™ radiosurgery, and the amount of radiation received.

Patients were excluded if their original pathology slides were unavailable for re-confirmation of diagnosis, or if they lacked comprehensive clinical information including presenting symptoms, tumor characteristics, treatment modality, disease recurrence, and dates of follow-up.

*Pathologic Determination of Grade*

Histopathological diagnosis of aPXA was independently confirmed by 3 senior neuropathologists (AP, AB, TT). Tumors were classified specifically as aPXA only upon agreement of 2 of 3 senior neuropathologists, with ambiguous cases excluded from our series to preclude the possibility of including misidentified tumors. Of ten patients initially identified with possible aPXA, 2 patients were excluded due to uncertainty over final diagnosis. Tumors were identified as aPXA if they demonstrated nuclear and cytoplasmic pleomorphism, xanthomatous astrocytic cells, multi-nucleated giant cells, and significant mitotic activity, defined as 5 or more mitoses per 10 hpf, and/or the presence of necrosis.

**Results**

*Patient Population and Tumor Characteristics*

The UCSF Department of Neurosurgery managed 8 patients with aPXA from 1999-2012 (Table 1). There was a female predominance in our cohort, with 5 female and 3 male patients. Our patients ranged in age from 4 to 74 years at time of diagnosis, with median and mean ages of 22 and 28, respectively. Tumor volumes averaged 61 $cm^3$, with a diameter ranging from 0.9 cm to 6.3cm. The most common presenting symptoms were seizure (50%) and headaches (25%). The great majority of aPXAs arose from the cerebral hemispheres, including the frontal (38%) and temporal (50%) lobes, with one tumor arising in the posterior fossa (13%). Two tumors (25%) were located in eloquent cortex, including the left supplementary motor area and the left frontotemporal lobes

*Histopathology*

The histopathologic characteristics of our patient cohort are summarized in Table 1 and depicted in Figure 1. By definition, all aPXAs demonstrated the presence of mitoses or necrosis, with 5 of 8 (63%) showing evidence of both. Five aPXAs (63%) additionally showed evidence of vascular proliferation. Three of 8 (38%) were $BRAF^{V600E}$ positive.

Of the patients with aPXA tumors, 3 had initially been diagnosed as primary PXA but underwent malignant transformation during their treatment course and were reclassified as secondary aPXA. Additionally, 2 patients first diagnosed with aPXA showed evidence of transformation into glioblastoma multiforme (GBM).

*aPXA Treatment Strategies and Outcomes*

Among the patients with aPXA, 6 received subtotal resection (STR), and 2 received gross total resection (GTR). Four of the STR patients received adjuvant therapy: 3 received XRT with chemotherapy, and 1 received chemotherapy alone. Regardless of the initial treatment strategy or

EOR, 7 of 8 patients suffered from recurrence or progression of their aPXA, the sole exception being a patient who has yet to receive a follow-up scan after their initial resection and diagnosis. Only 1 of 3 patients who underwent adjuvant XRT had a MRI available to review for treatment response, with no treatment response seen at 2 months post-XRT. The median time until recurrence or progression was 20 months, with a 1-year PFS rate of 57% (Figure 3).

Four patients went on to develop intracranial and/or spinal dissemination of their disease. The 3 patients who expired all showed evidence of dissemination at the time of their deaths. Overall follow-up times ranged from 1 month to 8.2 years, with a median survival of 87 months and a 1-year OS rate of 100% (Figure 2).

**Discussion**

Since its identification in 1979 by Kepes *et al.*, PXA remains a challenging tumor to classify. Due to its intrinsically pleomorphic appearance and variably indolent versus malignant clinical course, identification and differentiation from other low-grade gliomas are paramount to planning an effective treatment strategy. Importantly, recent research has been increasingly highlighting the manner in which anaplastic features render aPXA a markedly different neoplastic process.

Similar to other published series, our patients, with a median age of 22, tended to be younger than those with high-grade glioma. They also predominately developed tumors in the frontotemporal lobes, resulting in a majority of patients presenting with seizures (50%). Our experience, however, does also point to the fact that aPXA is not simply a diagnosis of children and young adults, as 4 of 8 (50%) patients were older than 30. Additionally, while PXA is

commonly considered a superficial supratentorial tumor,[7] our experience with an elderly patient who had a posterior fossa aPXA suggests that these tumors can present in atypical locations.

There were several clinical trends among our patient cohort. First, the majority of patients suffered from tumor progression. Second, all aPXA patients who received adjuvant therapy with radiation and/or chemotherapy suffered from tumor progression, suggesting these modalities may not provide adequate treatment of the residual tumor burden status-post STR. Third, adjuvant therapy had no discernable effect on preventing dissemination, as 3 of the 4 aPXA patients who suffered brain and spinal dissemination underwent prior radiation and/or chemotherapy to supplement their initial surgery.

Given the rarity of aPXA tumors, reports in the literature are scarce and many are limited in design to small case reports.[10,14-29] As a result, current understanding of aPXA tumors is incomplete. In one of the larger case series published on aPXA (33 patients), a multivariate analysis by Ida and colleagues demonstrated that OS was significantly lower in the aPXA cohort when compared to PXA. Tumors that had a mitotic index < 5/10 hpf or did not demonstrate necrosis yielded better survival outcomes. Of interest, there were no differences in PFS between aPXA and PXA.[30] In another study by Gallo *et al.*, aPXA tumors were similarly found to predict for poorer OS; however, unlike Ida *et al.*, they found an additional association with PFS.[31] Schmidt *et al.* described their experience in treating 10 aPXA tumors. Although the 5-year OS was less than 50%, their cohort did have 4 long-term survivors ranging between 7.5-11.9 years.[32]

Optimum treatment stratgies for aPXA are also not well-described. In an attempt to address predictors of outcome, Vu *et al*. performed a systematic review of the literature on both PXA and aPXA patients. Their analysis revealed that GTR was better than STR in prolonging PFS – but not OS – in PXA patients. However, they were unable to draw substantial conclusions

from the literature about outcome predictors among aPXA patients.[33] Thus, the role of EOR remains controversial.

In our series, of the 2 aPXA patients who underwent GTR, one suffered from recurrence. The remaining 6 patients with STR suffered from progression. Nevertheless, given the small sample size of our study, it is difficult to derive conclusions on whether GTR offers patients the best means of tumor control. Similarly, the utility of adjuvant therapy remains questionable: of the 4 patients who received postoperative XRT or chemotherapy, only 50% were alive by the end of the study. This observation is further strengthened by the finding that adjuvant therapies were completely ineffective in preventing residual tumor from progressing in patients who underwent STR. As such, unless the risk of morbidity is unacceptably high, we would thus advocate for aggressive EOR especially in cases where frozen intraoperative pathology is concerning for aPXA. Given that current therapies appear inadequate for preventing dissemination, reduction of initial tumor burden may also have prohibitive effects on future development of tumor spread throughout the CNS, though this remains speculation and would benefit from further study.

Examination of treatment strategies and clinical courses for aPXA patients suggests that the presence or absence of anaplastic features is not simply a pathologic distinction, but a feature that results in divergent patient outcomes. In our series, poor clinical outcomes were associated with aPXA. About 50% of our aPXA patients showed evidence of tumor dissemination, with 4 patients suffering leptomeningeal, intraparenchymal, and spinal drop metastases. In one of the few other studies stratifying clinical outcomes based on PXA and aPXA pathology, Vu and colleagues reported aPXA recurrence-free survival of 53% and OS of 82.3% at 1 year, with recurrence-free survival of 33% and OS of 50% at 5 years.[33] For PXA, they report a 5-year survival rate of 81-86%, and a recurrence-free survival rate of 49-72%.[7,8,33] Other studies

examining the significance of anaplastic features on patient outcomes additionally note their association with poor prognosis. Tumor mitoses and necrosis have each been associated with worsened OS,[6,7,33-35] and mitotic activity has been associated with earlier recurrence and poorer survival even when accounting for EOR.[7] In one such study, 9 of 15 deaths were noted to be associated with the presence of histological necrosis.[6]

The potential for PXA to transform into a higher grade tumor underscores the importance of interval follow-up for patients. Three of the 8 aPXAs transformed from an initial diagnosis of PXA, in one case even after the patient received an apparent GTR, and 2 aPXA patients demonstrated tumor transformation into GBM. Such cases raise doubts about the concept of PXA as a largely static and indolent tumor with favorable prognosis. Despite the presence of patients who live decades after their initial diagnosis, the uniformly fatal nature of high-grade gliomas necessitates that patients undergo continued clinical and radiographic monitoring. In particular, for any patient suffering tumor recurrence or growth, suspicion should remain high for malignant transformation and/or progression. Repeat resection should always be followed by close pathological examination of tumor tissue to ascertain the presence or absence of anaplastic features, with comparison to previously obtained biopsy specimens when available.

Given the unclear role for adjuvant radiation and chemotherapy,[5,8,10,11,36-39] efforts are increasingly underway to understand the unique tumor biology of PXA, including a greater emphasis on molecular markers. Despite sharing an astrocytic background, it appears that PXA and aPXA do not frequently possess MGMT methylation, leading one group of investigators to raise doubts about the benefits of temozolomide chemotherapy for PXA. Other scattered case reports note some success with chemotherapy with carboplatin and vincristine for 2 patients with aPXA.[37,40] Larger series have been unable to determine a role, if any, for chemotherapy.[7,33,38]

Further study of cancer markers have validated the unique genetic background of PXA. In several analyses of the presence of TP53 mutations, only 6% of all cases (7 of 123) were found to be positive for the mutation, and amplificiations of *EGFR*, *MDM2*, and *CDK4* also appear to be absent.[41-43] Interestingly, $BRAF^{V600E}$ appears to be a common mutation among PXA, with several groups suggesting it be used as a molecular and diagnostic marker for PXA given its frequency of ~60% of the tumors studied and absence in high grade glioma and meningeal tumors.[44,45] The mutation has been shown to promote cell proliferation, differentiation, and survival via the RAS/RAF/MEK/ERK kinase pathway.[44] We examined the mutation among our aPXA population and found a slightly lower prevalance of 38%. Given the availability of agents that target BRAF such as PLX-4032 and HSP90 inhibitors, aPXAs may be candidates for such biologic therapy, offering an important new treatment modality, particularly in lesions unamenable to further surgery or unresponsive to radiotherapy and/or chemotherapy.

***Study Strengths and Limitations***

Our study contains only 8 patients and is retrospective, thus precluding meaningful multivariate analysis and may contain selection bias. Additionally, the variable length of follow-up data make it difficult to draw conclusions on best treatment strategies and outcomes, underscoring the importance of multi-institutional efforts to publish data on this rare tumor. Furthermore, our $BRAF^{V600E}$ prevalence may underestimate the true rate given increasing awareness and nonuniform testing for this alteration in aPXA. Finally, our clinical and tumor information was limited by only half our cohort having available data on tumor size.

## Conclusion

Accurate initial diagnosis of aPXA – often with the help of multiple experienced neuropathologists – is a critical step in the implementation of aggressive and proactive management strategies. Subtotally resected tumors tend to recur, and adjuvant therapies such as radiation and chemotherapy currently have unclear roles in the prevention of tumor progression or dissemination. Regardless of treatment strategy, anaplastic features are a poor prognostic marker, and call into question the inclusion of aPXA as a grade 2 lesion given the much poorer outcomes of aPXA patients. Long-term monitoring of all patients with PXA and aPXA is a critical step in patient treatment due to the potential for tumors to transform into higher grade lesions with uniformly fatal prognosis. Identification and therapeutic manipulation of molecular markers such as BRAF may provide an important next step in the development of new treatment strategies for patients with PXA and aPXA.

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**Figure 1. Histological Features of Typical and Anaplastic PXA.** A) Low-power magnification demonstrating solid tumor with pleomorphic nuclei, ample cytoplasm and glial phenotype. Focal perivascular inflammatory infiltrates can also be seen as in other glioneuronal tumors (original magnification x100). B) High-power magnification of giant, multi-nucleated pleomorphic cells with xanthomatous cytoplasm and large irregular nuclei with inclusions (original magnification X400). C) High-power magnification of eosinophilic granular body, typical feature of PXAs (original magnification X400). D) Medium-power magnification of reticulin staining demonstrating a rich reticulin network invested around individual and clusters of tumor cells (original magnification X200). E) Anaplastic histological features in some PXA is evidenced as necrosis in some examples in the absence of prior treatment (original magnification X200). F) Some anaplastic examples also demonstrate marked rhabdoid cell phenotype and abundant mitotic figures (original magnification X400).

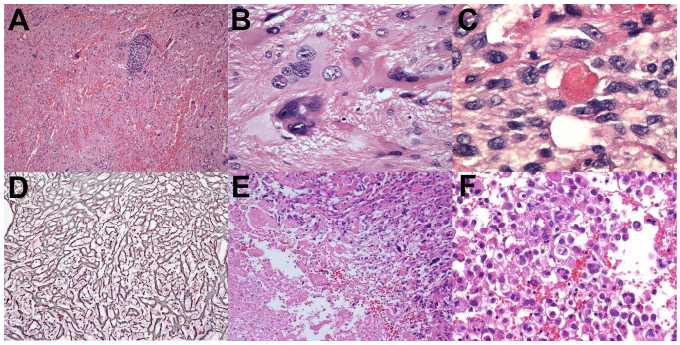
**Figure 2. Overall Survival for Patients with aPXA**

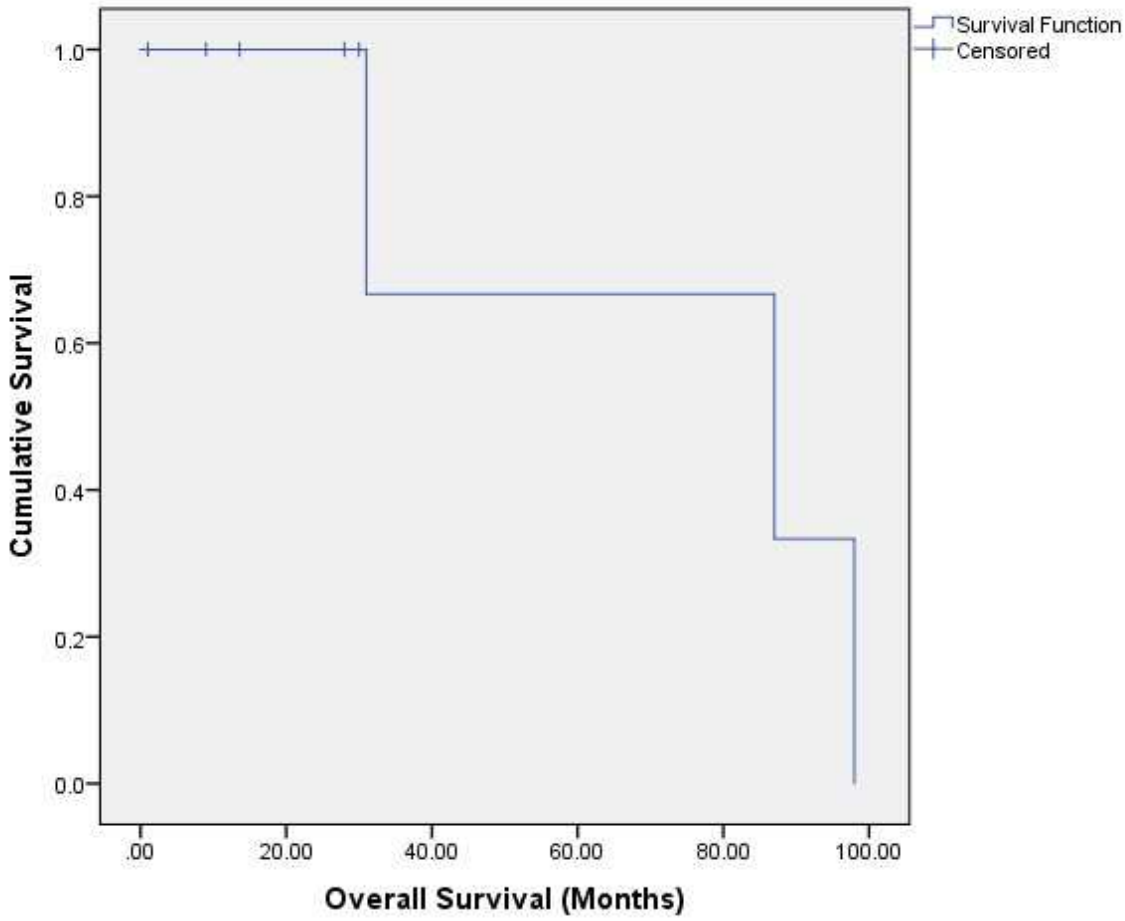
**Figure 3. Progression-Free Survival for Patients with aPXA**

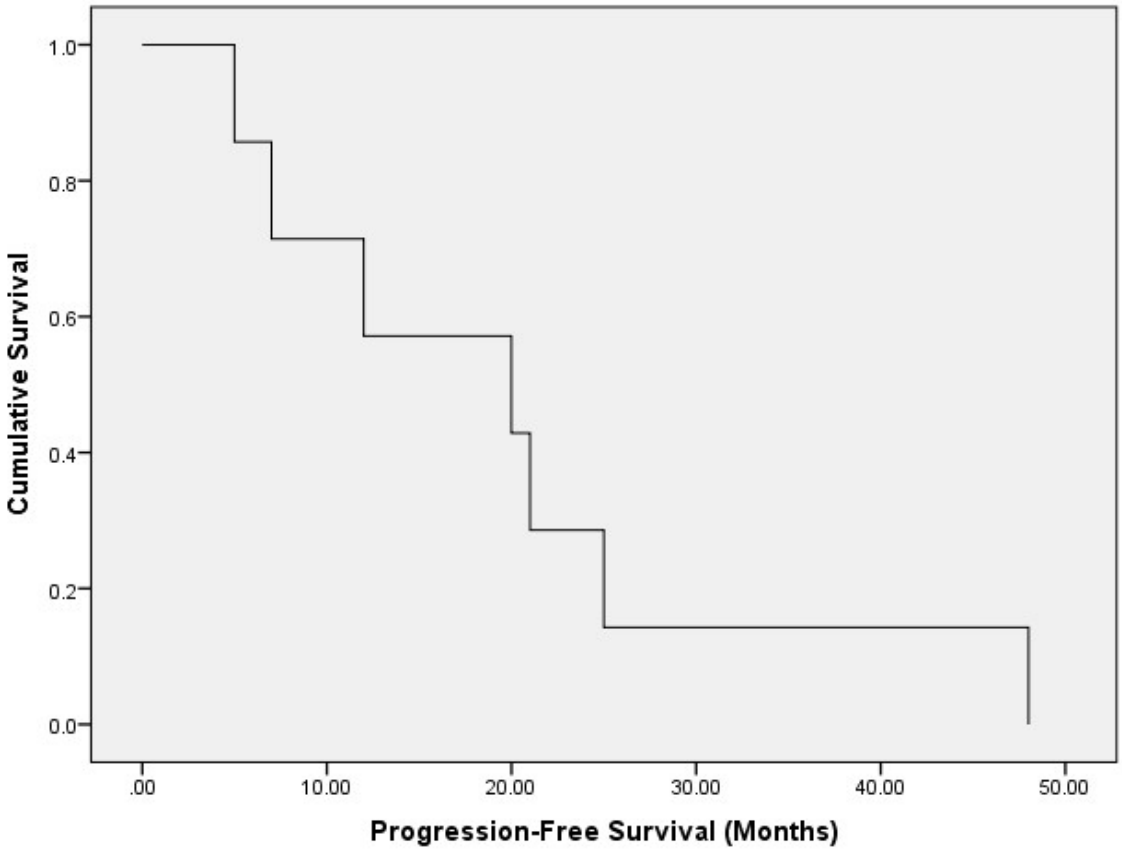
**Table 1. Clinical Characteristics, Diagnoses, and Treatment Outcomes for aPXA**

| Age/Gender | Location | Symptoms | Mitoses | Necrosis | Vascular Proliferation | EOR | Adjuvant | Progression | Malignant Transformation | CNS Dissemination | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 26/M | Temporal | Headache, Seizure | 1 | 2 | 1 | STR | XRT, Chemo | Yes | aPXA into GBM | IC | Expired |
| 17/M | Frontal | Headache | 1 | 1 | 0 | STR | XRT, Chemo | Yes | aPXA into GBM | IC | Expired |
| 4/F | Temporal | Seizure | 1 | 1 | 1 | STR | Chemo | Yes | None | IC and Spinal | Alive |
| 4/F | Frontal | Hemorrhage | 1 | 1 | 1 | STR | - | Yes | PXA into aPXA | IC and Spinal | Expired |
| 9/F | Temporal | Seizure | 1 | 0 | 1 | STR | - | Yes | PXA into aPXA | None | Alive |
| 38/F | Frontal | Seizure | 1 | 2 | 0 | GTR | - | Yes | PXA into aPXA | None | Alive |
| 74/F | Posterior Fossa | Dizziness/Ataxia | 1 | 0 | 1 | GTR | - | No | None | None | Alive |
| 54/M | Temporal | Vision Loss | 0 | 1 | 0 | STR | XRT, Chemo | Yes | None | None | Alive |

Abbreviations: *aPXA* - Pleomorphic Xanthoastrocytoma with Anaplastic Features; *EOR* - Extent of Resection; *CNS* - Central Nervous System; *F* - Female; *M* - Male; *STR* - Subtotal Resection; *GTR* - Gross Total Resection; *XRT* - Fractionated Radiotherapy; *Chemo* - chemotherapy; *IC* - Intracranial




Survival Function
Censored
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
Overall Survival (Months)



1. aPXA is associated with worse clinical outcomes when compared to PXA tumors
2. Surgical resection, with GTR when possible, provides the mainstay of treatment for this disease, while the role of adjuvant chemoradiation still remains unclear.
3. Patients with PXA tumors must be monitored for extended periods of time due to the fact that these tumors can undergo malignant transformation.

Abbreviations: pleomorphic xanthoastrocytoma (PXA); anaplastic pleomorphic xanthoastrocytoma (aPXA); World Health Organization (WHO); central nervous system (CNS); overall survival (OS); high power field (hpf); University of California, San Francisco (UCSF); committee for human research (CHR); progression-free survival (PFS); glioblastoma multiforme (GBM); subtotal resection (STR); gross total resection (GTR);