

# Demography, Pattern of Care, and Survival in Patients with Xanthoastrocytoma: A Systematic Review and Individual Patient Data Analysis of 325 Cases

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## Abstract

**Objectives** Xanthoastrocytoma (XA) is a low-grade glial tumor seen in young adults, and there is lack of robust data on treatment of this rare tumor. In this systematic review and individual patient's data analysis, we aimed to look into the demography, pattern of care, survival outcomes, and prognostic factors in patients with both Grade II and III XA.

**Methods** A comprehensive search was conducted with the Medical Subject Heading terms: "Xanthoastrocytoma; Pleomorphic Xanthoastrocytoma; Anaplastic Xanthoastrocytoma; Xanthoastrocytoma AND treatment; and Anaplastic Xanthoastrocytoma AND survival" to find all possible publications.

**Results** A total of 325 individual patients from a total of 138 publications pertaining to XA were retrieved. Median age of the entire cohort was 19 years. About 56.1% of the patients underwent a gross total resection (GTR) and 31.4% underwent a subtotal resection. Nearly, 76.6% of the patients had a Grade II tumor and adjuvant radiation was delivered in 27.4% of the patients. Estimated 2- and 5-year progression-free survival (PFS) were 68.5 and 51.2%, respectively. Age, grade, and extent of surgery were significant factors affecting PFS. Estimated 2- and 5-year overall survival (OS) was 88.8 and 78%, respectively. The median OS for Grade II and Grade III tumors were 209 and 49 months, respectively. Age and extent of surgery were significant factors affecting OS.

**Conclusion** XA is a disease of young adults with favorable prognosis. Younger patients (<20 years), patients who undergo a GTR, and patients with a lower grade tumor have a better treatment outcome.

## Keywords

- ▶ meta-analysis
- ▶ survival
- ▶ xanthoastrocytoma

## Introduction

Xanthoastrocytoma (XA) was first described by Kepes et al in 1979 as a low-grade glial tumor seen in young adults. XA usually presents with seizures and includes Grade II and Grade III tumors with distinct clinical behavior. Though most of the tumors are reported to arise from temporal lobe, these tumors have been reported to arise from any part of the central nervous system. Maximal safe surgical resection is often considered the cornerstone of therapy. Adjuvant

therapy though advocated by many lacks consensus and merits a relook. However, the greatest limitation is the sporadic reporting of XA in the literature. In the absence of robust data, treatments are often based on local expertise and institutional protocol extrapolating data of other common glial tumors. Our earlier analysis was limited to patients of Grade II XA.<sup>1</sup> In this systematic review and individual patient's data analysis, we aimed to look into the demography, pattern of care, survival outcomes, and prognostic factors in patients with both Grade II and III XA.

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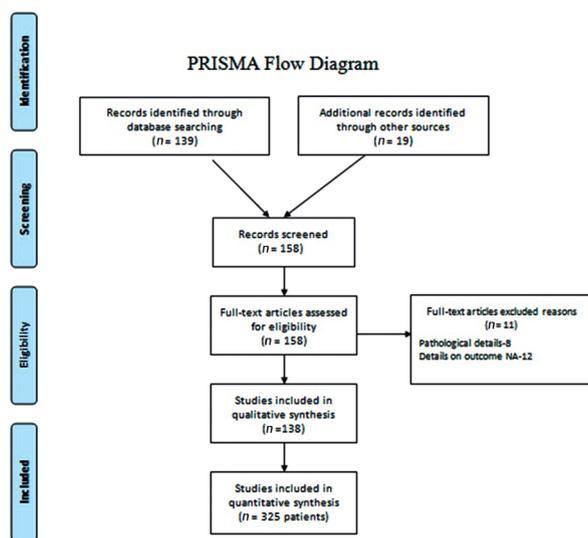
## Methods

### Search Methodology

A comprehensive search was conducted in the PubMed, Google Scholar with the Medical Subject Heading terms: "Xanthoastrocytoma; Pleomorphic Xanthoastrocytoma; Anaplastic Xanthoastrocytoma; Xanthoastrocytoma AND treatment; and Anaplastic Xanthoastrocytoma AND survival" to find all possible publications. After retrieving the titles of such articles, we sorted out any unrelated articles. We retrieved full-length articles of those remaining to finalize articles for data extraction. In addition, we searched the references in those articles as well to fetch any article missing after the search. Thereafter, duplicates were removed, and the remaining articles were looked into detail. Patient data were extracted and entered in a predesigned excel chart with the headings of "age, gender, presenting complaints, type of surgery, radiation use, chemotherapy, recurrence, duration of progression-free interval, salvage treatment, death, and survival." Articles that did not report treatment and outcome were excluded from the analysis. Once the data extraction was complete, it was rechecked by the individual authors to look for errors or duplication. A total of 138 articles were retrieved pertaining to XA with 325 patients.<sup>138</sup> The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (►Fig. 1) explains the data synthesis from the eligible studies.

### Statistical Analysis

The data were analyzed and categorical variables were summarized by frequency and percentage and quantitative variables by the median and range. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of diagnosis to the date of documented progression or death. Kaplan–Meier method was used to for survival analysis.



**Fig. 1** PRISMA flowchart showing summary of the search methodology and data collection for the meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Univariate analysis was performed using log-rank test, and Cox regression model was used for multivariate analysis. Factors with  $p$ -value  $< 0.1$  were included in the multivariate analysis. A  $p$ -value  $< 0.05$  was taken as significant. SPSS v.16 (SPSS Inc., Released 2007, SPSS for Windows, Version 16.0, Chicago, Illinois, United States) was used for all statistical analysis.

## Results

We retrieved data of 325 individual patients from a total of 138 publications pertaining to XA. Median age of the entire cohort was 19 years (range: 0.9–84 years). More than four-fifth (82%) of the patients were diagnosed within the fourth decade. Of these 325 patients, incidence of XA was equally distributed among males and females with a ratio of 0.92:1 favoring females. Nearly half of the patients presented with features of raised intracranial pressure (47%) followed by seizure which was the presenting symptom in one-third of the patients. Out of 325 patients, 118 (36.3%) patients had tumor located in the temporal lobe only followed by multilobar (16%) disease and frontal lobe (9.8%). A total of 8 patients had tumor located in different parts of the spinal cord as well. Only two patients had leptomeningeal dissemination at diagnosis. Patient characteristics are summarized in ►Table 1.

### Treatment

Surgical details were available in 287 cases. Of these, 161 (56.1%) patients underwent a gross total resection (GTR) and 90 (31.4%) patients underwent a subtotal resection. Histologic grade was available in 218 cases. Of these, 167 (76.6%) patients had a Grade II tumor and the remaining 23.4% patients had a Grade III tumor. Median  $K_i$ -67 was found to be 5.6% (range: 1–33.2%). In 14 patients (58.3%) out of 24 available cases, BRAF mutation was noted. Adjuvant radiation was delivered in 77 (27.4%) patients, whereas 1 patient was treated with palliative radiation and salvage radiation was used in 19 (6.8%) patients. In the available reports, all patients received local radiation alone. Adjuvant chemotherapy was used in 37 (14.9%) patients. Chemotherapy regimen varied widely; but in the recent report, temozolomide has been found to be the preferred choice ( $n = 7$ ).

### Survival Outcome

Estimated 2- and 5-year PFS were 68.5 and 51.2%, respectively. In univariate analysis, younger patients ( $\leq 20$  years) found to have better PFS compared with elder patients ( $> 20$  years) (hazard ratio [HR] 2.26 [95% confidence interval [CI]: 1.3–4.0],  $p = 0.006$ ). Patients with a GTR had a significantly better PFS than those treated with a subtotal resection (STR) only (HR 2.19 [95% CI: 1.1–4.2],  $p = 0.019$ ). PFS was found to be significantly better for those with a Grade II tumor compared with those with a Grade III tumor (HR 3.18 [95% CI: 1.6–6.4],  $p = 0.001$ ) (►Fig. 2). Age, grade, and extent of surgery continued to be significant in multivariate analysis with HR of 1.9 (95% CI: 1.2–8.2,  $p = 0.007$ ), 2.0 (95% CI: 1.2–3.3,  $p = 0.005$ ), and 1.9 (95% CI: 1.1–3.2,  $p = 0.018$ ), respectively.

**Table 1** Demographic features and patterns of care in patients with pleomorphic xanthoastrocytoma

Patient characteristics	Number of patients (percentage)/(range)
Age	Median: 19 y (range: 0.9–84)
Sex (n = 318)	Male: 153 Female: 165 Male:female ratio: 0.93:1
Presenting symptoms (n = 229)	Seizure: 108 (47.2%) Headache: 76 (33.2%) Sensory symptoms: 26 (11.4%) Motor symptoms: 16 (6.9%) Hemorrhage: 3 (1.3%)
Radiological feature (n = 61)	Cystic: 44 (72.1%) Solid: 10 (16.4%) Solid-cystic: 7 (11.5%)
	Contrast enhancement: 35(57.3%)
K <sub>i</sub> -67 labeling index (n = 54)	Median: 5.6% (range: 1–33.2%)
Surgery (n = 287)	Gross total or near total resection: 161 (56.1%) Subtotal resection or debulking: 90 (31.4%) Biopsy: 6 (2.1%)
Grade (n = 218)	Grade II: 167 (76.6%) Grade III: 51 (23.4%)
BRAF mutation (N = 24)	Yes: 14 (58.3%) No: 10 (41.7%)
Radiation (N = 281)	Adjuvant radiation: 77 (27.4%) No adjuvant radiation: 184 (65.5%) Palliative: 1 (0.3%) Salvage RT: 19 (6.8%)
Chemotherapy (N = 249)	Adjuvant: 37 (14.9%) (TMZ, n = 7) Not used: 208 (83.5%) Salvage-4 (1.6%)
Salvage treatment (N = 76)	Surgery: 20 (26.3%) Radiation: 13 (17.1%) Chemotherapy: 2 (2.6%) Surgery + RT: 13 (17.2%) CT + RT: 7 (9.2%) Surgery + CT: 3 (3.9%) Surgery + RT + CT: 18 (23.7%)

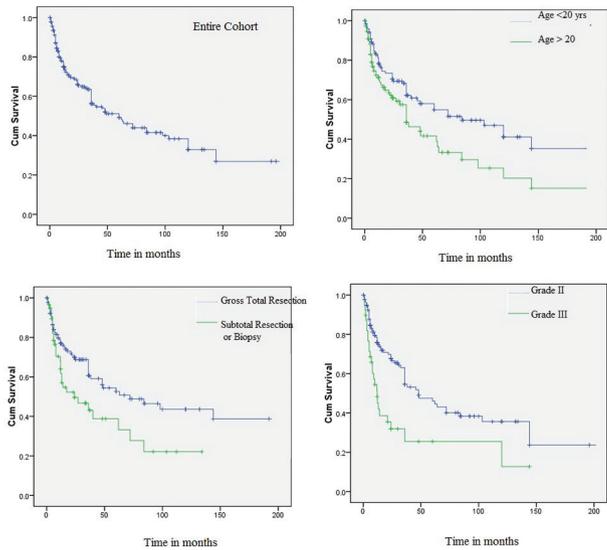
Abbreviations: CT, chemotherapy; RT, radiotherapy; TMZ, temozolomide.

Estimated 2- and 5-year OS were 88.8 and 78%, respectively. In univariate analysis, younger patients ( $\leq 20$  years) were found to have better OS compared with elder patients ( $> 20$  years) (HR 1.58 [95% CI: 1.07–2.32],  $p = 0.019$ ). Patients with a GTR had a significantly better OS than those treated with a STR only (HR 1.72 [95% CI: 1.1–2.71],  $p = 0.017$ ). OS was found to be significantly better for those with a Grade II tumor compared with those with a Grade III tumor (HR 2.2 [95% CI: 1.4–3.6],  $p = 0.001$ ) (► Fig. 3). The median OS for Grade II and Grade III tumors were 209 and 49 months, respectively. The other factors such as sex, adjuvant chemotherapy, and adjuvant radiotherapy had no impact on OS. Age and extent of surgery continued to be significant in multivariate analysis with HR of 3.4 (95% CI: 1.4–8.4,  $p = 0.005$ ) and 2.8 (95% CI: 1.3–6.3,  $p = 0.010$ ), respectively. Grade of tumor lost its statistical significance in multivariate analysis.

### Pattern of Recurrence and Salvage Treatment

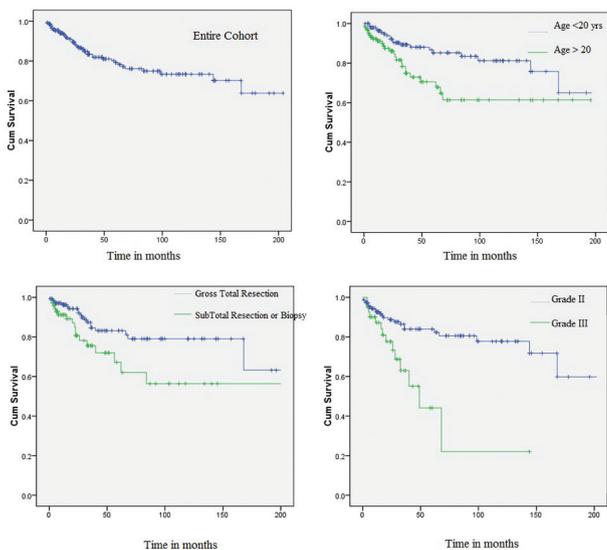
Status of disease progression was documented in 275 patients. At a median follow-up of 32.4 months, 130 patients experienced disease progression. Most common pattern of recurrence was local but 9 (6.9%) patients had leptomeningeal dissemination. Details of salvage therapy were available in 76 (58.5%) patients. About 26.3% patients underwent a repeat surgery alone, and 17.1% patients received radiation as salvage treatment. However, a total of 54 (71.1%) patients underwent surgery followed by observation or other form of therapy as well. Of these 76 patients, 51 (67.1%) received radiation either alone or in combination with surgery and chemotherapy. Interestingly, only 5 of these 51 patients had received prior radiation. Salvage chemotherapy has been used in 30 (39.5%) patients. Chemotherapy regimen varied widely from temozolomide, bevacizumab, carmustine, lapatinib, irinotecan, flutamide, lomustine, cyclophosphamide,

### Progression Free Survival



**Fig. 2** Kaplan–Meier curves showing progression-free survival in patients with xanthoastrocytoma for entire cohort, with respect to age, nature of surgery, and grade of tumor.

### Overall Survival



**Fig. 3** Kaplan–Meier curves showing overall survival in patients with xanthoastrocytoma for entire cohort, with respect to age, nature of surgery, and grade of tumor.

thiotepa, dabrafenib, etc. Interestingly, 4 patients were diagnosed with astrocytoma, glioblastoma, or anaplastic oligodendroglioma at recurrence.

## Discussion

XA has long been considered an indolent tumor entity. Because of the rarity of this tumor, there is a paucity of data regarding its clinical behavior and dilemma regarding the optimum treatment of these patients. In the absence of level

I evidence, the individual patient data analysis was formulated to describe the demography, pattern of care, and survival outcome for XA. The survival and prognostic variables for Grade II XA has already been described in an earlier article.<sup>1</sup> Hence, the present article aimed to compare survival and prognostic factors for Grade III XA with that of Grade II tumors as well. We retrieved 138 publications and derived individual patient data of 325 odd patients for the purpose of the analysis. Interestingly, only 7 publications had a sample size of more than 10.

For the entire cohort of XA, median age was 19 years. Our previous analysis of Grade II XA highlights the median age of 20 years which is not different for the entire cohort as well. This clearly reflects that XA is predominantly a disease of the young adults. The present analysis revealed an impressive median OS of 209 months for Grade II tumors, while it was only 49 months for Grade III tumors. An earlier analysis of Grade II and Grade III XA reported similar median survival.<sup>139</sup> Univariate analysis also pointed toward a better prognostic outcome for older patients (> 20 years) compared with the younger patients (< 20 years). Eighty-two percent of the cases are diagnosed up to the age of 40 years with isolated cases in different ages beyond 40 years.

A Surveillance, Epidemiology, and End Results (SEER) data analysis and our previous analysis highlight the importance of surgery in particular importance of achieving a GTR.<sup>139</sup> Although, in multivariate analysis, extent of surgery was not significant in the SEER analysis, it was significant in the analysis for Grade II tumors. The most important limitation of interpreting the surgical extent is variation of surgeons, different centers with variable experience, and in long period ways of interpretation of completeness of surgery. In addition, surgical standards have improved over the last few years with modern techniques such as intraoperative magnetic resonance imaging (MRI), awake craniotomy, and postoperative MRI. With the limitations of all these variables, the present analysis revealed significant impact of a GTR both on PFS (HR 2.19,  $p = 0.019$ ) and OS (HR 1.72,  $p = 0.017$ ). These findings clearly highlight the importance of achieving a GTR in XA. The analysis also highlights the importance of referring such patients to a center with expertise for better management.

However, the impact of adjuvant radiation was not a significant factor influencing OS or PFS. However, point should also be made that many of the patients have received radiation in poor performance status or with a large tumor. Furthermore, a possibility of publication bias cannot be ignored. This also highlights adopting a risk adopted treatment approach for lower and higher grade tumors. Hence, a GTR should be optimum for a lower grade tumor but a higher grade tumor merits more aggressive therapy with adjuvant radiotherapy or a combination of radiotherapy and chemotherapy should be advocated.

Because of excellent treatment outcome, long-term sequel and neurocognitive function is very important for these patients and every effort should be made to assure a better quality of life for patients with XA. In addition, follow-up protocol should also be carefully designed. As local recurrence is predominant, a contrast-enhanced MRI of brain

every 3 months for the first 3 years and thereafter 6 monthly for 2 years and then annually should be optimum.

In the recent years, great enthusiasm has been witnessed in exploring the molecular pattern of XA. Different reports have demonstrated nearly V600E BRAF mutation in nearly 70% patients which constitutively activates RAS/RAF/MEK/ERK signaling pathway. Different BRAF inhibitors such as vemurafenib and dabrafenib have shown promising results in the management of recurrent XA. The present analysis revealed 58% BRAF mutation rate which makes it an interesting target for recurrent cases.

The analysis reveals many important facts about the rare tumor. We found significantly improved survival outcome for patients treated with a GTR than those with STR. Similarly, both PFS and OS favored patients with a Grade II tumor, younger age. However, the impact of adjuvant therapy was not clearly beneficial. Note should be made that nearly 47.7% patients experience disease progression at a median follow-up of nearly 3 years. Hence, risk stratification should be done and adjuvant radiation and chemotherapy may be advocated for high-risk patients.

This analysis has few limitations as well. As the individual patient data has been extracted from publication over a long period of time, a temporal bias is paramount importance. In this time frame, diagnostic criteria, surgical skill, and treatment approach have changed which may have definite impact on the quality of report. In addition, the publications included in the analysis are retrospective which also add to different types of bias. Because of inhomogeneity in reporting the cases, all relevant data pertaining to each case were not retrieved. This also forced us to conduct analysis on available fraction of data for fewer parameters. The use of individual patient characteristics for analysis may be considered as one of the merits of this work.

## Conclusion

XA is a disease of young adults with favorable prognosis. Younger patients (< 20 years), patients who undergo a GTR, and patients with a lower grade tumor have a better treatment outcome. The role of adjuvant therapy is debatable. However, in Grade III and incompletely resected tumors, adjuvant radiation of a combination of both radiotherapy and chemotherapy should be delivered. Whole genome sequencing should be performed to identify patients with different clinical behavior and treat accordingly.

### Funding

None.

### Conflict of Interest

None declared.

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