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# Do Extent of Resection and Tumor Volume affect the Overall Survival of Anaplastic Astrocytoma? A Retrospective Study from a Single Center

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**Abstract**

**BACKGROUND:** Anaplastic astrocytoma (AA) is a rare brain neoplasm that belongs to grade III gliomas according to the World Health Organization classification. It represents only 6% of all central nervous system malignancies; yet, it is associated with low survival rates.

**AIM:** We aim to identify the survival rate after tumor resection from 10 years of experience. We also wish to determine the effect of pre- and post-operative tumor volumes on the overall survival (OS).

**METHODS:** We retrospectively reviewed the records of patients with AA who had surgery between January 2010 and January 2020. Based on magnetic resonance imaging results obtained <72 h after surgery, the extent of resection (EOR) was calculated by pre-operative volume – post-operative volume/pre-operative volume*100% and classified into five categories: (1) >99% – gross-total resection (GTR), (2) 91–99% as near-total resection, (3) 70–90% as sub-total resection, (4) <70% as partial resection, and (5) biopsy. A multivariate proportional hazards regression analysis assessed the independent association of EOR and subsequent OS.

**RESULTS:** Thirty-four patients were finally included in our analysis. The median survival time for all patients was 24.4 months, whereas the histopathological type of AA like isocitrate dehydrogenase enzymes (IDH) mutant was 32 months, and IDH wild type was 16.1 months as OS time. We stratified the observed survival durations for the patients according to the EOR into five different classes. We found that the EOR did not affect the overall median survival. Regression analysis showed no statistically significant association between the pre- or post-operative tumor volume and the OS time.

**CONCLUSION:** AA is a tumor that carries a poor diagnosis. GTR is essential to increase patients expected survival time. Unfortunately, the extent of tumor resection and tumor volume is not correlated with the survival time for patients.

## Introduction

Anaplastic astrocytoma (AA) is a malignant brain tumor that affects mainly adults. AA belongs to a group of malignant gliomas Grade III (the World Health Organization [WHO] Classification), including anaplastic oligodendroglioma. It is considered the first grade with histological evidence of malignancy after Grades I and II, which generally include tumors with a lower proliferative potential [1]. In a recent study that utilized the data of 21025 glioma cases from the Netherlands cancer registry, the incidence of glioma in adults was observed to increase in the past decade. They reported an increase in the incidence of gliomas from 4.9 cases per 100,000 in 1989 to 5.9 cases in 2010 [2]. More than half of the reported cases were histologically defined as astrocytoma. They also reported that the proportion of glioblastoma increased during the same period, while the proportion of anaplastic and unspecified astrocytoma decreased [3]. According to the WHO criteria for grading glial tumors, AA is defined by the following histopathological criteria: Nuclear atypia, increased cellularity, and significant mitosis without endothelial proliferation or necrosis, which are characteristic of glioblastoma [1], [4]. Its incidence is higher in males, with a higher incidence rate observed in adults aged more than 40 years (rate = 0.60) compared with children and adults aged (15 to 39 years) (rate= 0.09 and 0.26, respectively) [5]. The only established risk factors for this rare malignancy are exposure to ionizing radiation and rare syndromes such as neurofibromatosis type and tuberous sclerosis. Most of the AA cases arise from a previous lower-grade astrocytoma, while 25% of cases arise de novo. Like many other brain occupying lesions, it presents with a wide range of symptoms that depend mainly on the anatomic location of the mass and vary from sensory loss to personality changes and seizures. Magnetic resonance imaging (MRI) is the best imaging modality for diagnosing AA [4].

AA is a dangerous neoplasm; recent reports based on the Surveillance, Epidemiology, and End Results Program Registry have identified survival rates

for AA at 60.1% for 1-year survival and 25.9% for 5 years survival [3]. Treatment options for AA include surgical resection as the mainstay for treatment, radiotherapy, and even chemotherapy, which are proved beneficial for some recurrent cases [6], [7], [8]. Temozolomide is being widely studied to treat recurrent gliomas, including AA combined with chemotherapy [9], [10]. However, previous reviews have pointed to the lack of the primary data from prospective and randomized trials to discuss the advantage of resection over other treatment options. Our study used the records of the AA patients diagnosed and treated in our institution to identify the overall survival (OS) time after tumor resection. We also tested the correlation between the extent of tumor resection, the pre-operative tumor volume, and the post-operative residual volume with the OS time after follow-up.

## Materials and Methods

Between January 2010 and January 2020, 56 patients with AA were treated at Uzhhorod Regional Center of Neurosurgery and Neurology. We excluded 22 patients from statistical analysis who were lost on follow-up and those with incomplete records and cases under 18 years. The clinical data of 34 patients were reviewed retrospectively. Nineteen males (55.88%) with a mean age of 42.05 and 15 female (44.11%) with a mean age of 40.33 patients were included in our study. According to our inclusion criteria, these patients' data had the records and were included in the final analysis. Adults with AA (astrocytoma Grade III, determined histopathologically) underwent surgery at our center. They were followed for outcomes until January 2022. We enrolled patients with complete clinical data regarding patient's demographics, clinical history, radiographic findings, operative details, tumor characteristics, and pathological records.

### *Diagnosis and follow-up*

All cases were suspected of symptoms such as headache and focal neurological deficits. All patients with these clinical examinations underwent MRI preoperatively with and without gadolinium. An MRI scan was performed within 72 h after surgery in all operated cases. After the discharge from hospital, patients were followed up from 2 to 144 months (median – 36 months). In all cases, serial MRI was performed during follow-up. In addition, information about the post-operative quality of life and recurrence was collected through telephone interviews or clinical examination and imaging. MRI T1 contrast to show the abnormal mass, and then, the final diagnosis was documented after resection biopsy as indicated in the literature. Tumor volume was measured by independent neuroradiologist on pre-operative T1 contrast-enhanced MRI sequences. Three maximal diameters of the tumor were measured using axial (A), sagittal (B), and coronal (C) T1 contrast-enhanced scans, and tumor volume was calculated by volumetric method as; $V = (AxBxC/2)\ cm^3$. We acquired a second MRI scan (post-operative) within 72 h after the operation and then used the same volumetric approach to determine the post-operative volume. For follow-up, patients were followed until January 2022 using follow-up MRI for recurrence, clinical symptoms, and mortality. All the mortalities were double-checked by family members, phone calls, and messages.

### *Data management and analysis*

Pre-operation tumor volume (X) was classified by following group (1) <20 $cm^3$ (2) 20–50 $cm^3$ (3) 51–100 $cm^3$ (4) >100 $cm^3$, whereas post-operation tumor volume (Y) was classified as (1) 0.1–10 $cm^3$, (2) 10.1–50 $cm^3$, and (3) 50.1–100 $cm^3$. Based on pre-operative and post-operative volume, EOR was obtained by X-Y/X*100%. After obtaining EOR% again, we classified our data into (1) more than 99% as gross total resection (GTR), (2) 91–99% as Near-total resection (NTR), (3) 70–90% as sub-total resection (STR), (4) <70% partial resection, and (5) as biopsy. The primary outcome of our study was the OS period postoperatively. We used the available data to perform survival analysis by Kaplan–Meier test for AA patients. Survival time was measured in months since the operation and was stratified depending on the EOR during the surgery. A log-rank test was used to determine the effect of EOR percentage on survival. We also performed COX regression analysis models to assess the impact of pre- and post-operative volumes on the median survival time. For log-rank and omnibus test, $p < 0.05$ was considered a statistically significant value. We used the mean for survival time measured in months for continuous variables. The analysis was performed using Statistical Package for the Social Sciences, SPSS 25 edition.

## Results

After reviewing (56) records, 34 patients' records were finally included into our paper consisting of 19 males and 15 females. Mean age of male at diagnosis was 42.05 year. At the end of follow-up, total numbers of males alive were 5 (26%) and mortality rate (77%). Mean OS in males was 21.07 month, no of recurrence male 3. Mean age of females at diagnosis was 40.33 year. At the end of follow-up period, six females were alive with a mortality rate of 60%. Mean OS in females was 29.66 month, no of recurrence female 1. Histopathologically, 20 patient specimens

tested positive for isocitrate dehydrogenase enzymes (IDH) 1 mutations and their mean OS was 32 month, while 14 specimens carried that the IDH wild mutation with mean OS was only 16.18 month.

### *Survival outcomes*

Our analysis showed a difference in the median survival time according to the EOR percentage. Overall median survival time in all patients is 41 months (SE= 3.7). However, the median survival time for <70% resection volume of tumor was 34 months (SE= 23.6). In the 70–90% EOR percentage, the median survival time was 35 months (SE= 7.1), while in the <91–99% and >99% EOR percentage groups, the median survival time was 41 (SE= 3.5) and 70 (SE= 6.5) months, respectively (Figure 1).

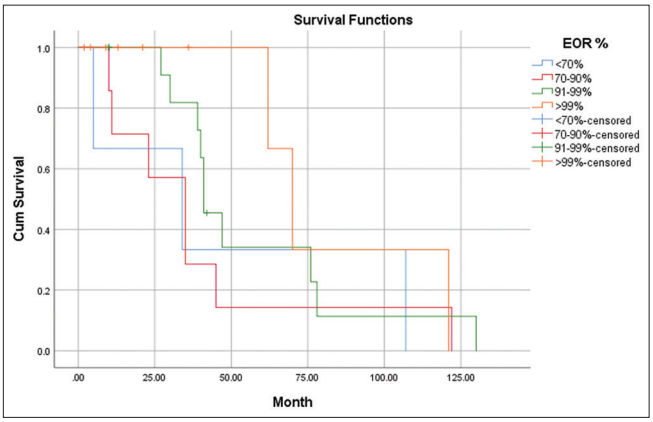


*Figure 1: Kaplan–Meier survival graph with EOR as factor variable for AA*

However, no statistically significant difference in survival time (months) according to the different EOR categories was detected (Log-rank test not significant, p = 0.446) (Table 1).

**Table 1: Log-rank test for EOR and survival for AA sheet**

| Overall comparisons | | | |
|---|---|---|---|
| | Chi-square | df | Sig. |
| Log-rank (mantel-Cox) | 2.667 | 3 | 0.446 |

Test of equality of survival distributions for the different levels of EOR %.

### *Regression models for pre and post-operative volumes*

The omnibus test for model validity was not significant ($\chi^2$ (3) = 4.134, p = 0.247) in case of pre-operative tumor volume. It shows that there is no association of pre-operative volume with survival rate. Consequently, all the pre-operative volume groups showed non-statistically significant association with the overall survival in these patients (Table 2).

**Table 2: Omnibus test for pre-operative volume and survival for AA sheet**

| Omnibus tests of model coefficients[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| –2 log likelihood | Overall (score) | | | Change from previous step | | | Change from previous block | | |
| | Chi-square | df | Sig. | Chi-square | df | Sig. | Chi-square | df | Sig. |
| 103.309 | 4.134 | 3 | 0.247 | 3.537 | 3 | 0.316 | 3.537 | 3 | 0.316 |

[a]Beginning block number 1. Method = Enter.

All the coefficients are not significant (p > 0.05). It shows that pre-operative volume has no influence on overall survival of the patients (Table 3).

**Table 3: Coefficients of pre-operative volume levels for AA**

| Variables in the equation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | B | SE | Wald | df | Sig. | Exp (B) | 95.0% CI for Exp (B) | |
| | | | | | | | Lower | Upper |
| Pre-operative vol group | | | 3.685 | 3 | 0.298 | | | |
| Pre-operative vol group (1) | –10.954 | 825.654 | 0.000 | 1 | 0.989 | 0.000 | 0.000 | 0. |
| Pre-operative vol group (2) | 0.959 | 0.554 | 2.990 | 1 | 0.084 | 2.608 | 0.880 | 7.730 |
| Pre-operative vol group (3) | –0.112 | 0.548 | 0.042 | 1 | 0.838 | 0.894 | 0.306 | 2.615 |

All the coefficients are not significant (p > 0.05). It shows that pre-operative volume has no influence on overall survival of the patients (Figure 2).

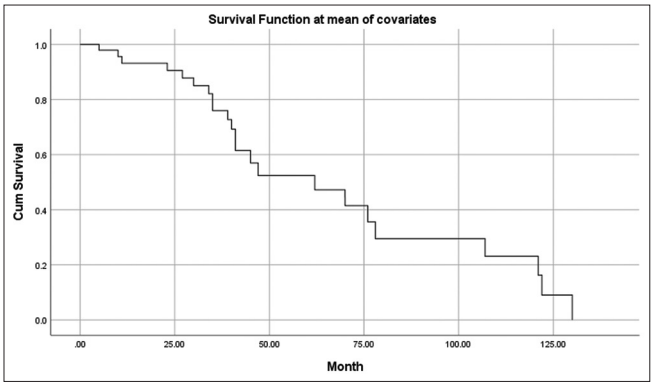


*Figure 2: Survival graph for pre-operative volume for AA*

Cox regression was performed to find out the impact of post-operative volume on the OS of patients. Omnibus test was significant ($\chi^2$ (1) = 4.008, p < 0.045) (Table 4).

**Table 4: Omnibus test for post-operative volume and survival for AA**

| Omnibus tests of model coefficients[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| –2 Log likelihood | Overall (score) | | | Change from previous step | | | Change from previous block | | |
| | Chi-square | df | Sig. | Chi-square | df | Sig. | Chi-square | df | Sig. |
| 99.931 | 4.008 | 1 | 0.045 | 6.915 | 1 | 0.009 | 6.915 | 1 | 0.009 |

[a]Beginning block number 1. Method = Enter.

However, the coefficients were not significant (p > 0.05). Furthermore, it shows no difference in survival time based on post-operative volume (Figure 3).

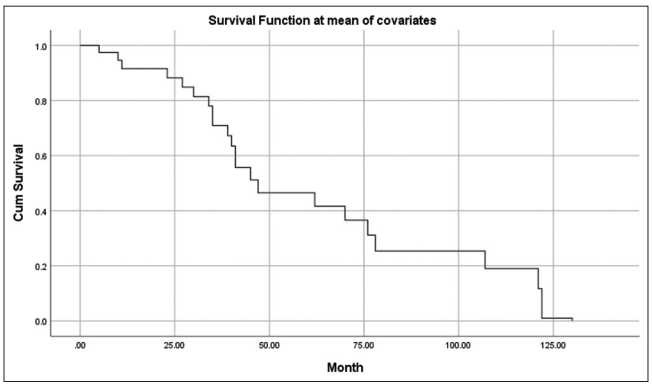


*Figure 3: Survival graph for post-operative volume for AA*

## Discussion

This report provided the median time for survival after AA tumor resection. Our analysis also showed that extent of resection (EOR) did not significantly affect the overall post-operative survival statistically. Interestingly, the tumour's pre-operative volume and post-operative residual volume were not statistically correlated with the overall median survival time.

Matehew *et al*. reported from 167 WHO grade III AA. Patients with the WHO Grade III astrocytomas did not live longer if they had a gross-total resection instead of NTR. For the WHO Grade III GTR, NTR, and STR, the median survival time after the first surgery was 58, 46, and 34 months [11]. In our cohort, the median survival time after resection was 41 months (SE= 3.7). This number is relatively more significant than the reported data in the literature, which is 2–3 years in most records [2], [3]. This may be explained by the relatively younger age of the population in our study, which was previously correlated with a better survival time [12]. Furthermore, the improvements in imaging modalities and better surgical techniques might have contributed to this finding.

We also reported that the EOR was not associated with a change in survival time. Although our sample is relatively small, these results are consistent with the previous report by Prados *et al*., who reported the same finding in a sample of 357 highly AA patients treated between 1977 and 1989. The median survival time reported in their study was 41.3 weeks compared to 41 months in our study. They also reported a significant correlation between survival time and younger patient age and the use of interstitial brachytherapy [12]. AA remains to be a terminal diagnosis. Due to the diffuse nature of the tumor, the recurrence rate is very high. The previous studies have utilized different strategies for improving survival rates. Based on our findings and the literature, although the EOR is not associated with a better survival time, it remains the sole most crucial step for treatment, mainly to improve pressure symptoms and delay the recurrence after radiotherapy. Our regression has not correlated the post-operative tumor volume with survival time ($p = 0.2$). This might be explained by the tumor's diffuse nature, which increases the recurrence of symptoms after mass removal [13].

It is important to mention that recent studies have correlated the survival duration to the histological signature of the tumor. The two main molecular categories of AA are IDH 1 mutated and IDH 1 wild type. IDH played an essential role in the pathogenesis of AA and other gliomas and affected OS [14], [15]. In RTOG 9402, a prospective and randomized trial assessed the OS benefit after using radiation therapy combinations in patients with anaplastic oligodendroglioma, IDH wild-type mutation was associated with a significantly reduced OS for all the treatment options compared with the IDH 1 mutation patients. They had nearly 5 times more survival time than the IDH 1 wild type patients [4], [16], indicating that the histological subtype element must be considered for all future studies. Cho U *et al*. reported all 11 patients with IDH1/2-mutated AA s lived for at least 5 years, but only 42% of patients with IDH1/2-wildtype AAs did [17]. For all of our patients, we used tissue histopathological analysis to identify the type of mutation. Our results showed that 20 patients representing 58.8% of our sample were classified as having IDH1 mutation, while the remaining 14 had the IDH wild mutation, which is supposed to produce more poor outcomes.

J.G. Hardie *et al*. reported in retrospective study of 184 people with AA and found that their OS was better if they had an IDH mutation, were younger, and had a tumor in the frontoparietal area [18]. We also noticed the relatively younger age of diagnosis in IDH1 mutated patients (mean age= 33.35) compared with wild type which had a mean age 52.75 in addition to the higher OS months detected in the IDH1 mutated patients 32 months compared with the IDH wild type (16.18 months). However, the presented data remain too small to draw a final association regarding the influence of these mutations on the OS.

This study provides evidence for a rare tumor that requires further investigation to improve the clinicians' understanding and knowledge. However, our results have some limitations such as the relatively small sample size which might have affected the power of the study to detect the differences between the study subgroups (sex, EOR), the lack of sufficient information about follow-up chemo and radiotherapy, and lastly, we did not correlate the detected survival rates with the detected mutation on histopathological examination.

## Conclusion

Our study demonstrates that the EOR for surgically treated AA is unrelated to total survival time. Furthermore, the pre-operative tumor volume does not correlate with the overall median survival time and the post-operative volume. Therefore, future studies should consider the mutant IDH type as a contributing factor to the clinical course of the disease and the expected survival, which might affect the treatment.

## Declarations

### *Ethics approval and consent to participate*

This study was approved by the Research Ethics Committee, Faculty of Medicine, Neurosurgery Department, Uzhhorod National University.

### *Availability of data and material*

The datasets used during the current study are available from the corresponding author on reasonable request.

### *Authors' contributions*

Study supervision: Volodymyr Smolanka, Andriy Smolanka, Taras Havryliv; Conception and design: Dipak Chaulagain; Statistical analysis: Dipak Chaulagain; First draft of manuscript: Dipak Chaulagain; Critical revision of the first draft: Andriy Smolanka; Revised submitted version: All authors; Approval of submitted version: All authors

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