

# The Outcome of Anaplastic Glioma Treated at a Tertiary Cancer Care Institute in South Asia

Arunkumar Madukkarai

Natarajan

Venkatraman Radhakrishnan

Alexander John

Department of Radiation Oncology, Cancer Institute (WIA), Chennai, Tamilnadu, India.

Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamilnadu, India.

Department of Radiation Oncology, Cancer Institute (WIA), Chennai, Tamilnadu, India.

**Objective:** Anaplastic glioma is a highly aggressive brain tumor that often occurs in young adults. There is a lack of data from India on anaplastic gliomas. This study aims to evaluate the prognostic factors of anaplastic glioma and correlate them with the outcome.

**Materials and Methods:** This is a retrospective observational study of 57 patients with anaplastic glioma treated from 1996 to 2015 in a cancer institute in Chennai. We captured data from the cancer institute's hospital-based electronic health record tumor registry and correlated factors including age, sex, histology, site of disease, type of surgery, adjuvant treatment, and radiation treatment technique with outcome. For the calculation of progression-free survival (PFS) and Overall Survival (OS), we used Statistical Package for Social Science (SPSS) software.

**Result:** This analysis included fifty-seven patients, with a median follow-up of 34 months. The median progression-free survival (PFS) and overall survival (OS) were 28 and 41 months, respectively. On univariate analysis, factors associated with improved survival include Anaplastic Oligodendroglioma histology (HR-0.43, CI-0.22-0.80, P=0.006), Frontal lobe location (HR-1.96, CI-1.07-3.58, P=0.025) Gross total resection (HR-1.94, CI-1.03-3.64, P=0.034), and addition of Temozolamide (HR-2.09, CI-1.14-3.84, P=0.014). On multivariate analysis Anaplastic Oligodendroglioma histology, (HR-0.49, CI-0.25-0.95, P=0.037), Frontal lobe (HR-2.14, CI-1.12-4.07, P=0.021), Gross total resection (HR-2.89, CI-1.47-5.69, P=0.002) and addition of Temozolamide (HR-2.02, CI-1.07-3.81, P=0.029) remained significant factors for improved OS.

**Conclusion:** Among the various clinical and treatment-related prognostic factors, our study revealed that anaplastic oligodendroglioma histology, frontal lobe location, gross total resection, and addition of temozolamide chemotherapy to radiation showed improved outcomes.

## Introduction

Primary brain tumors are rare, comprising 1-2% of all cancers. Of these, 80% of primary malignant tumors are gliomas [1]. Anaplastic gliomas (AG) which are classified as World Health Organization (WHO) grade 3 tumors, constitute 6.1% of all primary central nervous system gliomas. Anaplastic glioma includes anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma (AOA) [2]. These tumors often occur in young adults and typically recur or progress to grade 4 glioblastoma [3]. Some evidence shows anaplastic glioma is the molecular precursor of glioblastoma [3]. However, these tumors are often uncommon; anaplastic astrocytoma accounts for only 3.2%, and anaplastic oligodendroglioma is 1.2% of primary brain tumors compared with a 20.3% incidence with glioblastoma [4]. Anaplastic oligodendroglioma is a type of glioma that typically occurs in adults and is rarely seen in children. It often arises from oligodendrocytes, myelinating cells in the central nervous system. Oligodendroglioma has unique

histological features. It is classified as low-grade oligodendroglioma (Grade II) and high-grade oligodendroglioma (Grade III). Low-grade cells have pathological features of monotonous, regular, rounded, well-demarcated cells with abundant clear cytoplasm and a perinuclear halo, lending them an appearance that classically resembles “fried eggs.” These cells are often seen in conjunction with a background of a fine mesh of vasculature that is thought to resemble “Chicken wire.” High-grade glioma often arises from low-grade glioma and histologically resembles low-grade glioma except having features of mitotic figures, high cellular density, irregular cells, and endothelial hyperplasia and proliferation [5]. Anaplastic astrocytoma is a diffusely infiltrating tumor that arises from certain star-shaped brain cells called astrocytes. It is a rare and aggressive tumor. These astrocytes surround and protect other nerve cells found in the brain and spinal cord. Histologically characterized by nuclear atypia, increased cellularity, significant proliferative activity as manifested by mitoses, and a lack of endothelial proliferation or necrosis, the two pathological hallmarks of glioblastoma [6]. Exposure to ionizing radiation and genetic syndromes like neurofibromatosis type 1 and 2, tuberous sclerosis, and Li-Fraumeni syndrome are only established risk factors. The mixed oligodendroglial tumor has histological features of both oligodendroglia and astrocytic tumors [5].

Management is similar to that of glioblastoma multiforme (GBM). Anaplastic oligodendroglioma is often a chemotherapy-sensitive tumor and is different from anaplastic astrocytoma. This chemosensitivity appears to be linked to the loss of chromosomes 1p and 19q heterozygosity. Treatment of anaplastic astrocytoma has been less variable and often resistant to therapy. The median survival of this anaplastic astrocytoma is shorter, only two years, and as compared to anaplastic oligodendroglioma, it is usually five years [7]. Only limited evidence is available in the management of Anaplastic glioma. Treatment of Anaplastic glioma usually maximal safe resection and involved field radiation concurrent with Temozolamide identical to the management of glioblastoma. Owing to the rarity of the disease, it is difficult to study the factors that affect the long-term outcome of Anaplastic glioma. There is limited data from India on Anaplastic glioma. The primary objective of this study is to measure overall survival and progression-free survival. Secondary objectives to assess the prognostic factor include age, sex, histology, site of disease, adequacy of surgery, the addition of temozolamide, and radiation treatment technique were correlated with outcome.

## **Materials and Methods**

### **General study details**

It was a retrospective study of an individual electronic health record of patients with anaplastic glioma treated from 1996 to 2015. The Institute Ethical Committee (IEC) of the Cancer Institute approved the study on January 20, 2023. IEC project number is IEC/2023/ January 07. As it was a retrospective study, we exempted the requirement for informed consent. We ensured that we conducted the study per the ethical guidelines set by the Declaration of Helsinki and other guidelines such as Good Clinical Practice guidelines and those set by the Indian Council of Medical Research.

### **Inclusion/exclusion criteria**

Inclusion criteria include patients over 18 years of age, newly diagnosed anaplastic glioma, anaplastic astrocytoma, and oligodendroglioma treated with surgery and adjuvant chemoradiation. Exclusion criteria include metastatic disease, previous radiation, and non-anaplastic glioma histology.

### **Study methodology**

The evaluation included history, clinical examination, blood count, biochemistry, chest X-ray, and contrast-enhanced MRI (magnetic resonance imaging) of the brain. Patients underwent either biopsy or maximal safe resection. The adjuvant therapy was chemoradiation or only radiation, depending on the treating physician’s discretion. Adjuvant radiation included a daily dose of 200 cGy per day and a total dose of 60 Gy over 6-7 weeks. The Chemotherapy regime consisted of either oral Temozolomide (TMZ) 75mg/m<sup>2</sup>/day with cotrimoxazole prophylaxis half before radiation and 150mg /m<sup>2</sup>/day for 1- 5 days a month for six months after radiation or adjuvant PCV (procarbazine, carmustine, vincristine) regime after radiation. We assessed the response using contrast-enhanced magnetic resonance imaging.

We followed up with patients for three months in the 1<sup>st</sup> and 2<sup>nd</sup> year, six monthly in the 3<sup>rd</sup> to 5<sup>th</sup> year, and annually after that with clinical examination and imaging when indicated.

### Statistical Analysis

We calculated the progression-free survival (PFS) from the date of diagnosis until the date of progression, date of death, or date of last follow-up. Overall survival (OS) was calculated from the date of diagnosis until the date of death or the date of last follow-up and estimated by the Kaplan-Meier method. The Cox regression model was used to assess prognostic factors. We performed statistical analysis using SPSS version 20, and a p-value <0.05 was considered significant.

## Results

### General study-related details

We analyzed data from 57 patients with anaplastic glioma treated at Cancer Institute Chennai from 1996 to 2015. The baseline patient’s clinical characteristics are as mentioned in Table 1.

Variable	n	(%)
Age median (range)	36 (11-74)	
Sex		
Male	40	70
Female	17	30
Symptom		47
Headache	27	30
Seizure	17	23
Motor deficit	13	
Site		25
Parital	14	54
Frontal	31	21
Temporal	12	
Histology		
Anaplastic Astrocytoma (AA)	33	56
Anaplastic Oligodentrogloma (AO)	24	44
Surgery		
GTR	23	40
STR	31	55
Biopsy	3	5
Treatment		
CRT -TMZ/Adjuvant TMZ	27	47
RT -PCV	13	23

**Table 1. Baseline Patient Clinical Characteristics.**

The median age was 36 (range 11-74).

**Outcome**

The median PFS and OS were 28 and 41 months, respectively, and the five-year PFS and OS were 32.4% and 34.2%, respectively. The median OS of patients with AO and AA was 59 months and 17 months, respectively. The five-year OS of the patients with AO and AA were 50% and 18.8%, respectively.

**Factors affecting the outcome**

The factors included in the univariate analysis (Table 2) were age, sex, histology, site, type of surgery, treatment modality, and radiotherapy technique. Univariate analysis showed that AO histology (HR-0.43, CI-0.22-0.80, P=0.006), Frontal lobe location (HR-1.96, CI-1.07-3.58, P=0.025), Gross total resection (HR-1.94, CI-1.03-3.64, P=0.034), and addition of Temozolamide with radiation (HR-2.09, CI-1.14-3.84, P=0.014) had a significantly improved outcome.

Variable	Number	Median survival (months)	5-years OS (%)	HR	95% CI	P value
Age						
≤36	29	43	40.80	1		
>36	28	30	25.50	1.35	0.73-2.50	0.326
Sex						
Male	40	31	23.30	1		
Female	17	46	40.30	0.67	0.34-1.30	0.23
Histology						
AA	33	16	21.20	1		
AO	24	47	37.20	0.43	0.22-0.80	0.006
Frontal						
Yes	31	46	36.90	1		
No	26	18	19.20	1.96	1.07-3.58	0.025
Gross Total Resection						
Yes	23	53	47.00	1	1.03-3.64	0.034
No	34	30	15.30	1.94		
Temozolamide						
Yes	27	47	37.50	1		
No	30	16	20.00	2.09	1.14-3.84	0.014
Conformal						
Yes	27	44	33.40	1		
No	30	18	24.10	1.77	0.95-3.27	0.063

**Table 2. Univariate Analysis Evaluating the Factors that Affect the Overall Survival in Patients with Anaplastic Glioma.**

HR-Hazard ratio; CI-Confidence interval; OS-Overall survival

On performing the Multivariate analysis (Table 3), we found patients with Anaplastic

Oligodendroglioma histology (HR-0.49, CI-0.25-0.95, P=0.037), Frontal lobe (HR-2.14, CI-1.12-4.07, P=0.021), Gross total resection (HR-2.89, CI-1.47-5.69, P=0.002) and addition of Temozolamide (HR-2.02, CI-1.07-3.81, P=0.029) had a significantly improved outcome.

Variable	HR	CI	P
Histology			
AA	1		
AO	0.49	0.25-0.95	0.037
Frontal			
Yes	1		
No	2.14	1.12-4.07	0.021
Gross Total Resection			
Yes	1		
No	2.89	1.47-5.69	0.002
Temozolamide			
Yes	1		
No	2.02	1.07-3.81	0.029

**Table 3. Multivariate Analysis Evaluating the Factors Affecting the Overall Survival in Patients with Anaplastic Glioma.**

HR-Hazard ratio; CI-Confidence interval

Figures 1, 2, and 3 show the Kaplan-Meier curve for histology, surgery, and addition of Temozolamide.

**Figure 1. Kaplan-Meier Curve for Histology.**

**Figure 2. Kaplan-Meier Curve for Surgery.**

**Figure 3. Kaplan-Meier Curve for Temozolamide.**

## Discussion

Most published literature has combined the patients with AG and GBM, given rarity [3]. However, the biology of both tumors is different, and AG is a molecular precursor of GBM [3]. Anaplastic astrocytoma accounts for 3.2 %, and anaplastic oligodendroglioma is 1.2% of primary brain tumors compared with glioblastoma 20%. The prognosis depends on age, neurological deficit, and ECOG (Eastern Cooperative Oncology Group) performance status [4-7]. Our study showed that younger age ( $\leq 36$  years) and female sex had non-significant improvements in outcome. One study showed improved outcomes in young (age < 40 years) [8], while the other did not [9]. The female sex has a better outcome, possibly because of a tumor suppressor gene in the additional X chromosome [10].

Anaplastic oligodendroglial tumors had significantly improved survival as compared to anaplastic astrocytoma. The reason is that oligodendroglioma is chemosensitive [11], particularly those with 1p/19q co-deletion, with a median survival of more than ten years [12, 13]. Anaplastic astrocytoma has inferior survival as they are diffuse/ infiltrative, which makes complete resection technically

tricky.

Our study showed patients with frontal lobe tumors had a better 5-year OS. Some studies have shown that patients with frontal lobe tumors had better survival than patients with tumors located elsewhere [14-16], while others [9] did not. One possible reason is patients with tumors in the frontal lobe present earlier due to headache, seizure, or cognitive dysfunction. There is an association between 1p/19q co-deletion and tumor location [17].

In our study, the patients who underwent GTR had better survival than those who did not. For example, a study from Cleveland Clinic [18] showed that patients who underwent GTR/STR compared to those who underwent only biopsy had better survival.

In our study, patients treated with adjuvant chemoradiation followed by adjuvant temozolomide showed better outcomes. Deepthi Valiyaveetil [19] et al.'s study also showed that concurrent and adjuvant temozolomide patients had better survival rates. Emory McTyre [20] et al. showed that patients receiving radiation with temozolomide followed by adjuvant temozolomide had improved PFS and OS compared to those who received radiation followed by adjuvant temozolomide.

CATNON trial [21] that had patients without 1p/19q co-deletion showed that patients who received adjuvant temozolomide had improved survival. CODELtrial [22] that had 1p/19q co-deleted patients and is for RT followed by PCV versus TMZ concurrent with RT followed by adjuvant TMZ versus TMZ alone.

Our study is one of the first studies from South India to report the outcomes and prognostic factors for anaplastic glioma and confirm the findings reported in the literature. Limitations of our study include retrospective nature, single-center experience, small sample size, and lack of molecular information like IDH mutation, MGMT methylation, 1p19q co-deletion, ATRX, and CGIMP. They may be due to a preliminary study from a low-income country with limited resource access.

In conclusion, among the various clinical and treatment-related prognostic factors, our study revealed that anaplastic oligodendroglioma histology, frontal lobe location, gross total resection, and addition of temozolomide chemotherapy to radiation showed improved outcome.

## **Institutional Ethical Committee**

Approved

## **Conflicts of Interest**

There are no conflicts of interest.

## **Funding**

None.

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