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CLINICAL STUDY – PATIENT STUDY

Outcome and prognostic features in anaplastic ganglioglioma: analysis of cases from the SEER database

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Abstract Anaplastic ganglioglioma (AGG) are rare central nervous system tumours. Patient and treatment factors associated with outcome are poorly defined and limited to small retrospective case series and single case reports. Using the Surveillance, Epidemiology, and End Results (SEER) cancer registry, we investigated potential clinicopathological factors that can affect outcome in patients with anaplastic ganglioglioma. Patients with anaplastic ganglioglioma diagnosed between 1973 and 2007 were identified from the SEER database. Kaplan–Meier survival analysis and Cox models were used to examine the effect of variables on overall survival. The variables analysed included patient age at diagnosis, gender, race, tumour location, uni-focal or multi-focal tumour, surgical resection and the use of adjuvant radiotherapy. Fifty-eight patients were identified, with a median age at diagnosis of 25.5 years. Ninety-three percent of patients underwent surgery and 36% received adjuvant radiotherapy. The median overall survival was 28.5 months. The most common tumour site was the temporal lobe (27%). Univariate and multivariate analysis identified surgery and uni-focal disease as important predictors of overall survival. Adjuvant radiotherapy did not influence overall survival. This study represents the largest analysis of anaplastic ganglioglioma to date. Furthermore it also emphasises the role of national tumour databases for furthering our understanding of rare brain tumours and determining management options.

Keywords Anaplasia · Ganglioglioma · SEER · Epidemiology · Survival

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Introduction

Gangliogliomas were first described as a distinct type of intracranial neoplasm in 1926 and they represent approximately 0.4–1.0% of all brain tumours [1, 2]. They are classified as grade I tumours according to the World Health Organisation (WHO) classification of brain tumours. Histopathologically these tumours are comprised of ganglionic and glial cells and are thought to arise from glioneuronal precursor cells capable of differentiation to both glial and neuronal components. The proportion of each component varies in individual cases [3, 4]. Gangliogliomas can occur anywhere throughout the central nervous system, however, most occur supratentorialy, predominantly in the temporal lobe [5]. These tumours are highly epileptogenic [3, 6, 7], are more prevalent in the children and young adults [5] with a slight preponderance in males [1].

Anaplastic gangliogliomas are rare tumours [4, 5, 8–11] and are categorised as grade III according to the WHO classification [18, 19]. The anaplastic transformation usually occurs in the glial component, although there are reports of changes within the neuronal component [4, 13–16] as well as sarcomatous change [3, 17]. Histologically,

these tumours have areas of hypercellularity, mitotic figures, vascular proliferation and necrosis [18]. Anaplastic gangliogliomas typically present as de novo tumours (20–24), but up to 10% of cases [3, 5] undergo malignant transformation of a previously benign ganglioglioma [24–31]. Anaplastic transformation is more common in the paediatric population [14] and has been associated with previous subtotal tumour resection and radiotherapy [2, 32, 33].

The National Cancer Institute's Surveillance, Epidemiology, and End Results database (SEER) is considered the gold standard of all cancer registries. This database provides researchers with data that are sufficiently powered to conduct statistical analysis to characterise rare tumours. Due to the paucity of anaplastic ganglioglioma cases in the literature, we have utilised the SEER database to investigate the epidemiology, natural history and prognostic factors to further our understanding of these rare tumours.

Methods

Information was extracted from the SEER database which is maintained by the US National Cancer Institute. SEER-STAT version 6.6.2 (Surveillance Research Program, National Cancer Institute, Bathesda, MD, USA) was utilised to extract the data. The SEER 17 Registries (1973–2007) dataset was utilised. All patients with anaplastic ganglioglioma diagnosed in this period were identified. The International Classification of Diseases for Oncology (ICD) code (Anaplastic Ganglioglioma: 9505/3) was used. Statistical analysis was performed using Intercooled STATA 8.0 (STATA Corporation, 4905 Wakeway Drive, College Station, Texas, USA) software.

Kaplan–Meier survival analysis was used to assess the overall survival (OS). Patients were censored if they were lost to follow up or if the event (death) did not occur at the end of the observed period. Only death was considered as an event. The Mantel-Cox log-rank test was utilised to determine differences in the survival curves. Univariate and multivariate Cox proportional hazard models were utilised to determine the hazard ratios (HR) and their 95% confidence intervals (CIs). This was done to ascertain the effect of individual variables on overall survival. Only statistically significant variables in univariate analysis were considered for multivariate analysis. Possible explanatory clinical variables assessed included age at diagnosis, sex, race, tumour location, uni-focal versus multi-focal disease, surgical resection and the use of adjuvant radiotherapy. Ethical approval or informed consent was not required for this study as the SEER database contains fully anonymised data.

Results

Patient and tumour characteristics

Between 1973 and 2007, 58 patients were registered on the SEER database with a diagnosis of anaplastic ganglioglioma with an incidence rate of 0.02 cases per million per year. The incidence rates for male and female cases are 0.013 and 0.005 cases per million per year respectively. The distribution of patients divided according to region is displayed in Table 1. Median follow up period for all for all observations including censored cases was 52 months (range, 2–335 months) with a median age at diagnosis of 25.5 years old. The patient, tumour and treatment characteristics are displayed in Table 2. These tumours showed a significant male predominance and occurred in younger patients below the age of 40 years old. The temporal and frontal lobes were the most common location.

Factors associated with survival

Univariate analysis identified surgery ($P = 0.002$) and number of lesions ($P = 0.005$) as factors associated with prognosis (Table 3). Age of diagnosis ($P = 0.01$) and tumour location ($P = 0.01$) although significant, the confidence interval included the null value therefore these P values are invalid. In multivariate analysis (Table 4), surgery ($P = 0.01$) and uni-focal disease ($P = 0.001$) emerged as predictors of survival. Again tumour location ($P = 0.007$) although significant, the confidence interval included the null value therefore the P value is invalid. A total of 21 patients (36.2%) received adjuvant radiotherapy and there was no statistically significant survival benefit from radiotherapy.

The 5 year survival rate was 63% (95% confidence interval 46.0–76.0) and the median overall survival was 28.5 months. Kaplan–Meier curve illustrating overall survival for the full cohort can be seen if Fig. 1a. Kaplan–Meier survival curves demonstrate that in patients undergoing surgery had better prognosis compared to those who

Table 1 Number of patients divided according to region

State	Number of patients
California	26
Connecticut	3
Georgia	5
Iowa	4
Kentucky	1
Louisiana	2
Michigan	7
New Jersey	9

Table 2 Patient, tumour and treatment characteristics

	N (%)
Patient characteristics	
Age	
0–15	18 (31.1)
16–39	27 (47.2)
40–49	5 (9.2)
50–59	6 (9.3)
60–69	1 (1.1)
>70	1 (1.1)
Sex	
Male	41 (70.0)
Female	17 (30.0)
Race	
White	49 (84.2)
Black	4 (7.4)
Others	5 (8.4)
Tumour characteristics	
Location	
Fontal	13 (22.1)
Temporal	15 (26.6)
Parietal	4 (6.1)
Occipital	5 (8.2)
Brain Stem	3 (5.5)
Cerebellum	1 (2.1)
Spinal cord	5 (8.2)
Overlapping	12 (21.2)
Number of primaries	
1	54 (92.9)
2	4 (7.1)
Treatment characteristics	
Surgery	
Yes	54 (92.9)
No	4 (7.1)
Radiotherapy	
Yes	21 (35.8)
No	37 (64.2)

Table 3 Univariate analysis on the effect of patient, tumour and management factors on overall survival (hazard ratio ± confidence interval)

Univariate analysis				
Variable		Hazard ratio	Confidence Interval	Overall *P*-value
Gender	Male	1.00†		0.121
	Female	0.3665354	0.10–1.30	
Race	White	1.00†		–
	Black	–	–	
	Others	–	–	
Location	Frontal	1.00†		0.010**
	Temporal	1.23	0.13–11.98	
	Parietal	3.24	0.20–51.91	
	Occipital	–	–	
	Brain Stem	1.76	0.11–28.98	
	Cerebellum	–	–	
	Spinal	0.01	–	
	Overlapping	–	–	
Age per decade	0–9	1.00†		0.011**
	10–19	0.86	0.17–4.36	
	20–29	0.78	0.16–3.90	
	30–39	0.28	0.03–2.69	
	40–49	4.45	0.55–35.72	
	50–59	2.11	0.43–10.49	
	60–69	–	–	
	70–79	–	–	
Surgery	No	1.00†		0.002*
	Yes	0.17	0.05–0.52	
Radiotherapy	No	1.00†		0.480
	Yes	0.69	0.24–1.95	
Number of lesions	One lesion	1.00†		0.005*
	Two lesions	6.43	1.75–23.57	

† Reference category

* Statistically significant

** Invalid *P* value as confidence intervals covers the null value indicating non-convergence of statistical model

did not have surgery (Fig. 1b). Patients with uni-focal tumour had a better prognosis compared to those with multi-focal disease (Fig. 1c). In summary, patients with frontal uni-focal tumours undergoing surgery had the best prognosis.

Discussion

The biological behaviour of anaplastic ganglioglioma is poorly understood due to their rarity and the current literature evidence is limited to case series and individual case reports [8, 20–23]. The incidence and prevalence remains unknown, however, they tend to occur in an older population than their low grade counterparts [12]. In a series of ten cases for which clinical details were available, six patients died of tumour progression within 5–26 months of initial diagnosis, and those with a frontal tumour location had better prognosis [6]. In a series of five cases Majores et al. reported a 60% recurrence rate and 53% 5 year survival rate (median follow up 38 months). In this series all five patients underwent surgical resection with only one patient receiving radiotherapy and chemotherapy and further two patients receiving only radiotherapy [7]. Blumcke et al. reported a recurrence rate of 38% in his cohort of

Table 4 Multivariate analysis on the effect of patient, tumour and management factors on overall survival (hazard ratio ± 95% confidence interval)

Multivariate analysis				
Variable		Hazard ratio	Confidence interval	Overall *P*-value
Location	Frontal	1.00†		0.007**
	Temporal	–	–	
	Parietal	1.94	–	
	Occipital	–	–	
	Brain Stem	–	–	
	Cerebellum	1.85	–	
	Spinal	2.04	0.18–23.53	
	Overlapping	3.64	0.43–30.65	
Surgery	No	1.00†		0.012*
	Yes	0.17	0.05–0.68	
Number of lesions	One	1.00†		0.001*
	Two	96.93	8.03–1170.51	
Age per decade	0–9	1.00†		0.227
	10–19	2.25	0.25–20.14	
	20–29	0.59	0.07–5.33	
	30–39	0.13	–	
	40–49	–	–	
	50–59	–	–	
	60–69	–	–	
	70–79	–	–	

† Reference category

* Statistically significant

** Invalid *P* value as confidence intervals covers the null value indicating non-convergence of statistical model

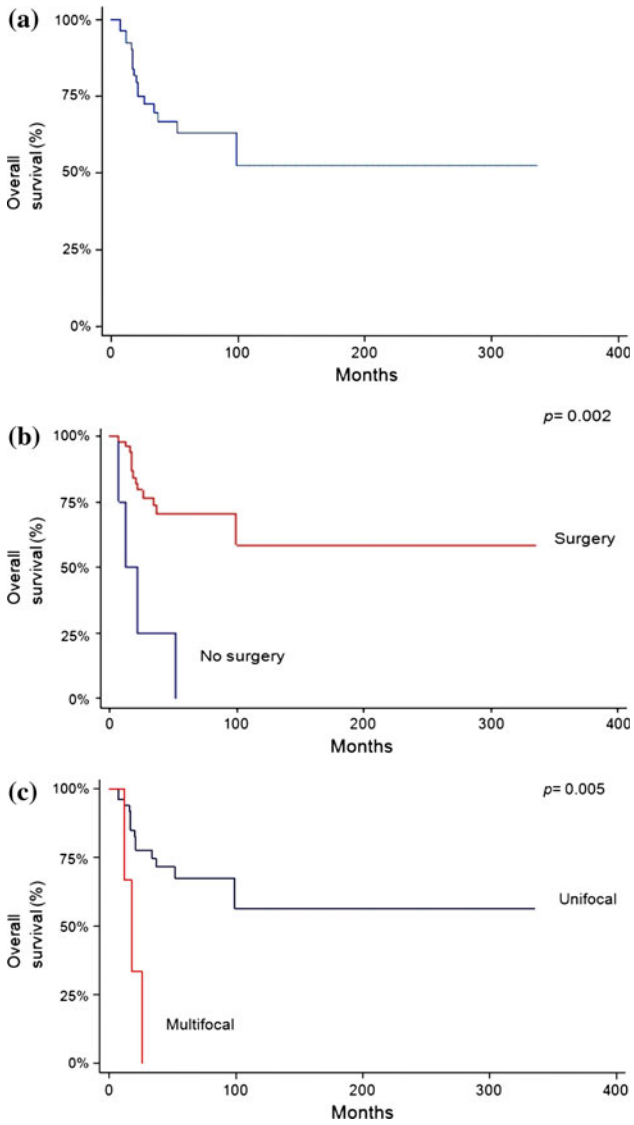

Fig. 1 Kaplan–Meier curves showing overall survival for **a** the full cohort; **b** according to surgical resection; and **c** separated into unifocal or multi-focal disease

eight patients (median follow up 120 months) [34]. All eight patients underwent surgical resection, however, no information was available with regards to whether they received adjuvant treatment.

In summary, the current clinical management of anaplastic gangliogliomas is based in retrospective cases series and case reports, and there is limited data on prognostic factors and prognosis. Utilising the large number of patients provided by the SEER database, this study investigated epidemiology, natural history and prognostic factors that affect outcome in patients with anaplastic ganglioglioma.

Patient and tumour characteristics

In our study the most common site for the occurrence of these tumours is supratentorially with the temporal lobe being the common site; cerebellum anaplastic gangliogliomas are rare. Interestingly this distribution is also true for the low-grade ganglioglioma [1, 35–39], and our data agrees with previously published series and isolated case reports [7, 31, 34]. This distribution may reflect the fact that most of these tumours occur secondary to malignant transformation of a previously low grade ganglioglioma. In our series 78% of the patients were below the age of 40 years old. Interestingly gangliogliomas also has predilection for the young adult population [5]. However, it was noted that the anaplastic cases tended to occur in the older population. In our series the median age of diagnosis was 25.5 years old which is higher that the reported median age of gangliogliomas of 23 years old reported in the literature [7, 40]. Interestingly 70% of patients in our sample were males. This male predilection is also true for several published series of ganglioglioma cases [1, 7]. In the series of five patients published by Majores et al. of anaplastic

gangliogliomas 80% of patients were males [7]. Karremann et al. in his series of eight children also found increased male predilection of the ratio of 5:3 [39]. Interestingly this predilection is also seen in paediatric high grade gliomas [39].

Factors associated with survival

In both univariate and multivariate analysis site is not an important predictor of survival. In both the above analyses the *P* value was not consistent with the confidence interval indicating a non-convergence of the statistical model. Interestingly previous isolated case studies reported patients with frontal anaplastic ganglioglioma had no recurrences following surgical resection without radiotherapy [6]. However, in contrast, a study of eight anaplastic gangliogliomas by Karremann et al. revealed that tumour location did not affect prognosis [39], however, this was in paediatric cases only. Age at diagnosis was also not an important predictor of survival on both univariate analysis and multivariate analysis. Most published series did not identify age as a prognostic factor, [6, 7, 12] although some authors report that age $\geq$40 years is associated with a shorter overall survival [7]. Gender was not a predictor of survival in this study, although there was a trend towards a poorer prognosis in males, which is consistent with previous studies [35], although in a review of eight cases by Karremann et al. gender was not a statistically significant factor [39]. Unsurprisingly our study also revealed that patients who presents with multifocal disease has poorer prognosis. Interestingly there have not been any previous case reports in the literature of multifocal anaplastic ganglioglioma. As a result this variable has not been assessed prior to this as a prognostic marker in the context of anaplastic ganglioglioma. In our series four patients from the SEER database had multifocal tumours, which serve to highlight the benefit of a national tumour database for studying rare tumours.

Tumour management

For anaplastic gangliogliomas gross total tumour resection is associated with a better prognosis [18, 19, 25, 39, 41], which was confirmed on both univariate and multivariate analysis in our study. This reflects the increasing literature evidence that maximal safe tumour resection should be undertaken for all high-grade gliomas [42]. However, the benefit of radiotherapy and chemotherapy is still being debated for anaplastic ganglioglioma [18, 19, 24]. However, the evidence for the benefits of surgical resection should be interpreted with caution as selection bias is not eliminated from the above retrospective analysis as patients were not randomised. Patients who have had surgery may have been younger and with more accessible unifocal lesion. Whilst it is accepted that radiotherapy should be used in grade I gangliogliomas undergoing malignant transformation [18], the current literature reveals limited evidence on the benefits of using adjuvant treatments like for these tumours [6, 10, 18, 36]. Indeed, two case reports of anaplastic ganglioglioma treated with gross total resection without adjuvant treatment have reported prolonged patient survival without tumour recurrence [10, 20]. In our study, there was no statistically significant difference in overall survival between those patients who underwent adjuvant radiotherapy and those who did not. However, there was a trend towards longer survival in patients who received adjuvant radiotherapy and the lack of statistical significance may reflect the small sample size.

Limitations of the SEER database

The SEER database provides invaluable data on rare brain tumours and enables analyses of large series than would otherwise be possible from institutional studies. However, the database has limited information on tumour size, extent of resection, dose and type of radiotherapy and the use of chemotherapy. There was no data available on time to tumour recurrences (which would enable calculation of progression free survival), performance status complications or co-morbidity. Given the recently developed prognostic factors for other gliomas, for example in glioblastoma performance status, age, extent of resection and MGMT status, [43], the omission of these factors is a limitation of this study. Nevertheless, this is the largest series to date and considering the rarity of this tumour is the best evidence currently available. Furthermore given the rarity of anaplastic gangliogliomas, the pathological diagnosis has not been subjected to scrutiny by an independent pathologist. Nevertheless despite several shortcomings our study is the most thorough analysis of anaplastic gangliogliomas to date and provides relevant prognostic and management insights to these rare tumours. Despite its anaplastic features these tumours appears to exhibit clinical behaviour similar to its low grade counterpart. The anecdotal observations from published case series and isolated case reports are confirmed by our study.

Conclusions

Our data suggests that patients with anaplastic ganglioglioma may benefit from surgical resection since this is positive prognostic indicator. The role of adjuvant radiotherapy remains to be defined—certainly there was no survival advantage compared to those who did not receive it. Additionally, overall survival is better in uni-focal

tumours. This study also highlights the role of national cancer databases for furthering our understanding of rare brain tumours and deciding on management options.

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