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ORIGINAL PAPER

Impact of surgery, adjuvant treatment, and other prognostic factors in the management of anaplastic ganglioglioma

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Abstract

Background/purpose Anaplastic ganglioglioma (AGG) is a rare tumor with both glial and neuronal component accounting for less than 1% of all CNS tumors with limited information about the optimum treatment and outcome of these tumors.

Method and materials We did a thorough search of the PubMed with the following MesH terms: "Ganglioglioma; Anaplastic ganglioglioma; Ganglioglioma AND treatment; and Anaplastic ganglioglioma AND survival" to find all possible publications related to AGG to perform an individual patient data analysis and derive the survival outcome and optimum treatment of these tumors.

Results A total of 56 articles were retrieved pertaining to AGG with 88 patients. However, a total of 40 publications found eligible with 69 patients for individual patient data analysis. Median age for the entire cohort was 16 years (range 0.2–77 years). Surgical details were available for 64 patients. A gross total or near total resection was reported in 21 cases (32.8%), subtotal resection or debulking was reported in 25 cases (39.1%). Surgical details were available for 64 patients. A gross total or near total resection was reported in 21 cases (32.8%), and subtotal resection or debulking was reported in 25 cases (39.1%). Median overall survival (OS) was 29 months [95% CI 15.8–42.2 months] with 2- and 5-year OS 61 and 39.4% respectively.

Conclusion AGG is associated with a dismal. Pediatric age and a gross total resection of tumor confer a better progression-free survival and OS. Hence, surgery should remain the cornerstone of therapy. However, because of modest survival, there is enough opportunity to improve survival with addition of adjuvant radiation and chemotherapy. A whole genome sequencing and molecular characterization would help to derive the best treatment option.

Keywords Anaplastic ganglioglioma · Surgery · Radiotherapy · Chemotherapy · Survival

Introduction

Ganglioglioma (GG) was first described in 1926 as a rare central nervous system tumor accounting for 0.4–1% of all brain tumors [1]. As the name suggests these tumors are composed of both ganglionic and glial component. GG have been described to arise from all part of the central nervous system but more commonly from the temporal lobe. These highly epileptogenic tumors are often diagnosed in young children and adults presenting with intractable epilepsy. Because of the indolent disease course, WHO has defined GG as grade I. However, these tumors sometimes show an aggressive clinical course and defined as anaplastic ganglioglioma (AGG) which are considered WHO grade III [2]. A surgical excision is considered standard of care for AGG and a maximal safe resection is the aim of surgery [3, 4]. However, even after a surgical complete tumor removal, many patients experience recurrence. Hence, many centers recommend adjuvant radiation or chemotherapy or a combination of both for optimizing tumor control and improve survival [4, 5]. Even after multimodality treatment survival is often poor. However, owing to the rarity of these tumors, most of the data is derived from institutional practice, case reports, or small case series with the limitation of wide range of bias. Hence, we embarked on to do an individual patient data analysis to find the optimum treatment of these tumors. So, the question we asked was "Whether adjuvant therapy has a role in the management of AGG." We planned to derive basic patient characteristics, treatment details, and survival information from all published studies of AGG and analyzed the impact of treatment.

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Search methodology

We did a thorough search of the PubMed with the following MesH terms: "Ganglioglioma; Anaplastic ganglioglioma; Ganglioglioma AND treatment; and Anaplastic ganglioglioma AND survival" to find all possible publications related to AGG. Once we identified the references, we went through all the abstracts to select the articles which have reported clinical information of AGG. After preliminary shortlisting the abstracts, we extracted full text of those articles and archived for data extraction. We also conducted a detail search of the references in the available article to retrieve missing articles and also conducted a hand search in Google to find any possible publication. After a thorough search, duplicates were removed and remaining articles were looked into detail. Individual patient data were tabulated in excel chart with the following headings: age, gender, surgery, type of surgery, radiation and type of radiation (local/craniospinal radiation), chemotherapy, recurrence, duration of disease-free interval, death, and overall survival. Articles which described about the pathological, molecular, and other factors only unrelated to treatment and outcome were excluded from the data extraction. After data extraction, the excel chart was reviewed by the authors independently to rule out any duplication. A total of 56 articles were retrieved pertaining to AGG with 88 patients. However, only 40 articles furnished adequate information related to 69 individual patients of AGG eligible for the present analysis. The PRISMA flow chart (Fig. 1) explains the data synthesis from the eligible studies.

Statistical analysis

The data were analyzed; categorical variables were summarized by frequency and percentage, and quantitative variables by the median and range. Progression-free survival [PFS] and overall survival [OS] was calculated from the date of diagnosis to the date of documented progression or death. Univariate analysis was performed using log-rank test to find the impact of prognostic variables on PFS and OS. The Kaplan-Meier method was used to for survival analysis (Fig. 2). Univariate analysis was done to find an impact of age, gender, type of surgery, use of radiation, and use of chemotherapy on survival outcome. A p value of < 0.05 was taken as significant. SPSS v16. (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.) was used for all statistical analysis.

Results

A total of 56 articles were retrieved pertaining to AGG with 88 patients. However, a total of 40 studies found eligible with 69 patients for individual patient data analysis [1, 4–58]. Median age for the entire cohort was 16 years (range 0.2–77 years). Out of these 88 patients, 45 (51.1%) were found of the pediatric age group. Out of 88 patients, 43 were male and 33 female with a male:female ratio of 1.3:1, suggestive of a male preponderance; gender of 12 patients were not available. Presenting symptom was available in 56 patients; headache was the commonest symptom (37.5%) followed by seizure (34.6%). Tumor location was available for 65 patients, 53 intracranial, and 12 spinal lesions. The patients' characteristics have been summarized in Table 1.

Surgical details were available for 64 patients. A gross total [GTR] or near total resection was reported in 21 cases (32.8%), and subtotal resection [STR] or debulking was reported in 25 cases (39.1%). Information regarding adjuvant radiation was available in 65 cases, whereas it was not clearly mentioned in 23 cases. Out of these 65 cases, radiation details were available for 17 cases. Local radiation was used in all 9 patients with available information of radiation volume. Information regarding use of chemotherapy was available for 53 cases only; out of these 53 patients, chemotherapy was used in 28 (52.8%).

A total of 20 patients experienced recurrence. Pattern of recurrence was predominantly local; however, two patients experienced a spinal dissemination, and one of these two patients had cervico-dorsal lesion and the other had right parieto-occipital lesion at the beginning. In addition, one patient with a frontal lesion experienced extracranial dissemination.

Survival outcome

After a median follow-up of 12 months (range 1–132 months), median PFS of the entire cohort was 24 months [95% CI 9.7–38.2 months]. Estimated 2- and 5-year PFS was 47.5 and 30% respectively. In univariate analysis, pediatric patients had median PFS of 34 months [95% CI 7.3–60.6 months] compared to 15 months [95% CI 9.8–20.2 months] for adult patients but failed to reach statistical significance. Patients undergoing a GTR were found to have better PFS [42 months, 95% CI 11.1–72.9 months] compared to those with a STR [9.2 months, 95% CI 0.0–30.1] without statistical significance Fig. 2. However, other factors like gender, use of adjuvant radiation, or chemotherapy were not found to have any impact on PFS.

Median OS was 29 months [95% CI 15.8–42.2 months] with 2- and 5-year OS 60 and 39.4% respectively. In univariate analysis, pediatric patients had median OS of 42 months [95% CI: NR] compared to 24 months [95% CI 20.4–27.6 months] with a trend towards statistical significance ($p = 0.091$). Patients undergoing a GTR were found to have significantly better OS [132 months, 95%: NR] compared to those with a STR [22 months, 95% CI 10.8–33.2] or those with an unknown surgical extent [34 months, 95% CI 14.4–53.6 months] ($p = 0.008$). Patients with tumor in cerebral

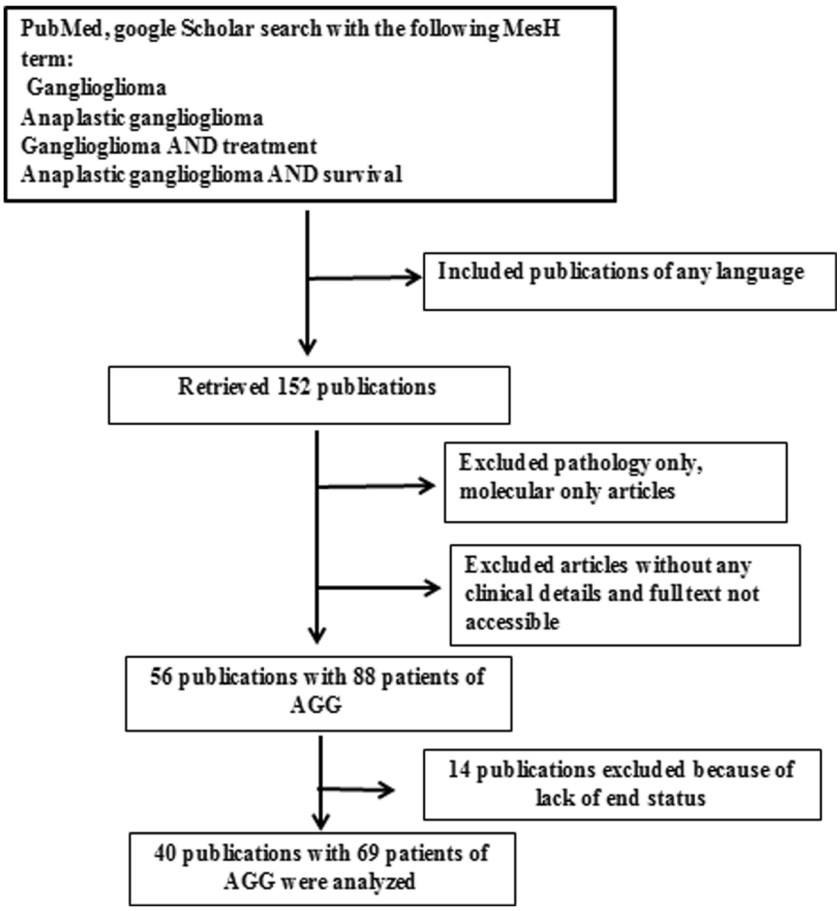

Fig. 1 The flow chart showing summary of the search methodology for AGG

hemisphere or single-lobe involvement had a better OS of 132 months [132 months, 95%: NR] compared to those with a multilobe involvement or disease in infratentorial and spinal location [34 months (95% CI 19.7–48.3 months); $p = 0.032$] (Fig. 3). However, other factors like gender, use of adjuvant radiation, or chemotherapy were not found to have any impact on OS.

Discussion

Gangliogliomas were described as a distinct entity in 1926 representing 0.4–1.0% of all brain tumors [1]. WHO has recognized ganglioglioma of two distinct grades depending of biology viz., ganglioglioma (grade I) and AGG (grade III) [2]. These tumors are composed of both glial as well as

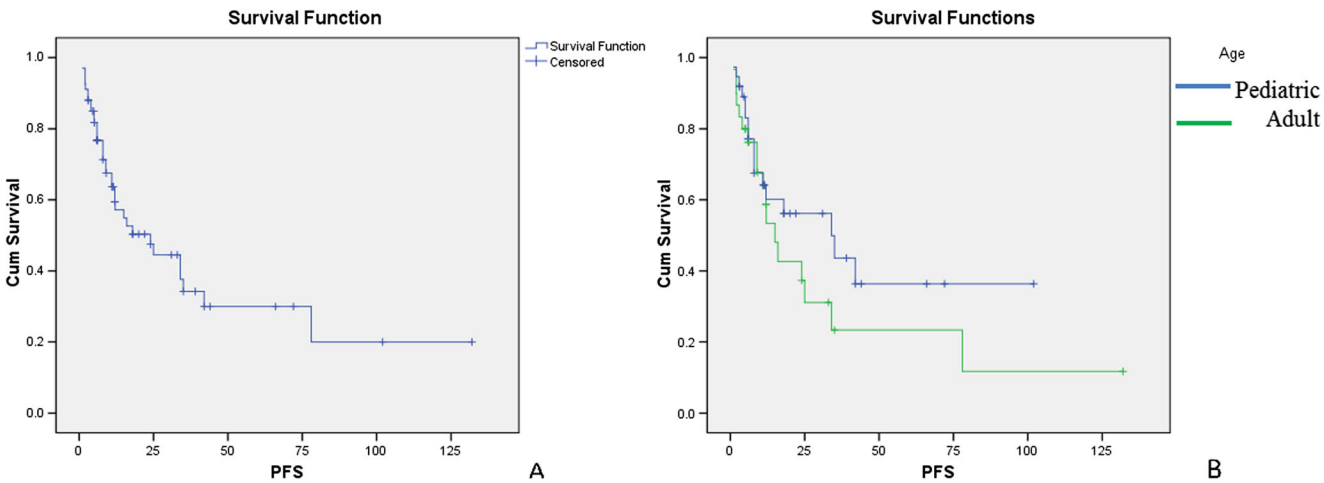

Fig. 2 Kaplan-Meier curves showing progression-free survival in patients with AGG (**a**) and impact of age on PFS (**b**)

Table 1 Demographic features and patterns of care in patients with AGG

Patient characteristics	Number of patients [percentage]/[range]
Age $n = 88$	Median—16 (range 0.2–77 years)
Sex $n = 76$	Male—43
	Female—33
	Male:female ratio of 1.3:1
Presenting symptoms $n = 56$	Headache—22 (39.3%)
	Seizure—19 (33.9%)
	Motor symptoms—7 (12.5%)
	Cerebellar—8 (14.3%)
Tumor location $n = 65$	Frontal lobe—10 (15.4%)
	Parietal lobe—4 (6.2%)
	Temporal lobe—14 (21.5%)
	Multiple lobe—7 (11.1%)
	Infratentorial—11 (16.9%)
	Spinal—12 (18.5%)
	Basal Ganglia—2 (3.1%)
	Meninges—1 (1.5%)
Surgery $n = 64$	Gross total or near total resection—21 (32.8%)
	Subtotal resection or debulking—25 (39.1%)
	Biopsy—3 (4.6%)
	Unknown—15 (23.1%)
Radiation $n = 65$	Adjuvant radiation—49 (75.4%)
	No adjuvant radiation—16 (24.6%)
Chemotherapy $n = 53$	Used—28 (52.8%)
	Not Used—25 (47.2%)

ganglionic component which arises from glioneuronal precursor cells and in few occasions de-differentiates to higher grade tumor. AGG is a rarer tumor of the GG group with more aggressive clinical and biological course than the other subtypes. The rarity of AGG is easily understandable by the fact that this comprehensive literature search could yield only 56 articles of AGG with 88 patients and only 40 studies with 69 patients were eligible for individual patient data analysis [1, 4–58]. These tumors found mostly affecting children and young adults with reported median age of 25 years at diagnosis [3, 4]. In the present analysis, median age was 16 years (range 0.2–77 years) which shows a predilection of AGG in younger patients. This finding is further supported by our finding that nearly half of the patients are of pediatric age. Adding a new insight, we found patients of pediatric age group to have a better PFS [34 vs 15 months] and OS [42 vs 24 months, $p = 0.091$] but could not reach statistical significance because of small sample size. Though AGG is known to arise from any part of the central nervous system, temporal lobe has been reported to be the commonest location [3]. A SEER database analyses by Selvanathan et al. reported 27% patients to have temporal lesion followed by 22% in the frontal lobe. In the present analysis, also 21.5% patients had a temporal lesion followed closely by frontal lesion. Interestingly, the SEER report found only 8.2% patients with a spinal lesion, but in the present analysis, 18.5% patients were found to have a lesion in the spinal cord.

Though, an earlier report correlated better survival for patients with a frontal tumor and worse for temporal tumor, the present analysis could not make such an observation. However, the present analysis revealed better OS for patients with disease in cerebral parenchyma and single-lobe involvement compared to those with multilobe disease or infratentorial and spinal location. This may be because of ease of surgical resection in cerebral parenchymal disease or single-lobe involvement compared to spinal, infratentorial, or multilobe involvement. Location of the tumors correlates well with the presenting symptom as well with nearly one third patient presented with headache and seizure each which emphasizes the importance of keeping ganglioglioma as an important differential in younger patients presenting with seizure or headache.

Surgery plays pivotal role in symptom reduction and allows tissue diagnosis. A reliable diagnosis of ganglioglioma compared to AGG is of paramount importance as AGG is associated with a poorer survival outcome and merits a multidisciplinary adjuvant therapy for improving disease control and survival. In the present analysis, nearly one third patients underwent a gross total resection and another one third patients underwent a STR which can be because of eloquent tumor location. When we looked into the survival outcome, PFS was better for patients with a GTR [42vs 12 months] but failed to reach statistical significance. However, patients with a GTR had a significantly better OS [132 vs 22 months, p—0.008] compared to those with a STR or unknown surgical extent. This clearly emphasizes that

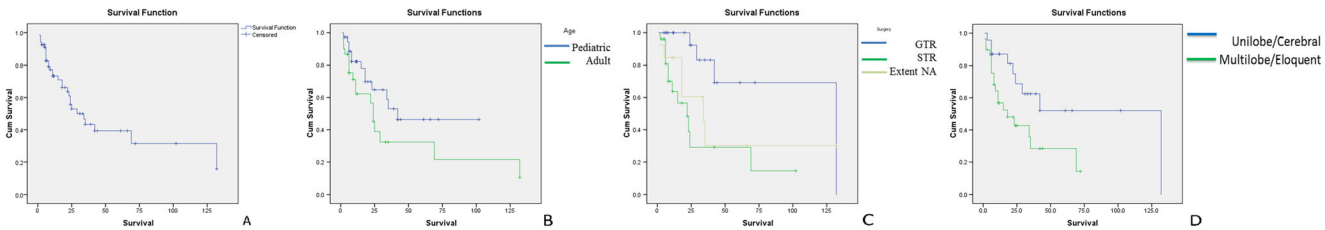

Fig. 3 Kaplan-Meier curves showing overall survival in patients with AGG (**a**), impact of age (**b**), impact of extent of surgery (**c**), and location of tumor (**d**) on OS

surgery should be aimed at achieving a GTR whenever feasible without causing functional compromise and consolidates the observation of Selvanathan et al. and Terrier et al. of a better survival for patients undergoing a GTR compared to those with a STR [3, 4]. The importance of preoperative imaging also is crucial which should be able to derive important information regarding the tumor behavior and help to proceed with a GTR. The newer functional imaging, perfusion and diffusion images may be of great help in this regard. The higher grade and anticipated aggressive behavior of tumor help favorably to decide for adjuvant therapy for AGG across institutes. Because of lack of evidence, many institutes advocate the ongoing adjuvant treatment policy for other high-grade glial tumors for AGG as well. Hence, 75.4% patients received adjuvant radiation with a median dose of 56 Gy (range 40–66 Gy). Because of glial origin and predominantly arising from the cerebral parenchyma, a local radiation has been considered in the available literature. Liauw et al. reported better disease control in ganglioglioma when treated with adjuvant radiation after a STR. Terrier et al. reported a trend towards better survival for patients treated with adjuvant radiation [4]. In addition, the authors observed best survival outcome for patients treated with a GTR followed by adjuvant chemoradiotherapy further emphasizing the role of adjuvant therapy ever after a GTR. In addition to radiation, 52.8% patients in the present analysis received different forms of adjuvant chemotherapy. However, our analysis failed to elicit any advantage of adjuvant radiation and chemotherapy as well. But, note should be made of the fact that we are analyzing a rare disease where 71 patients data have been extracted from 42 studies. Hence, there is every possibility of different biases and errors which should be looked into carefully. The mode of diagnosis, quality of reporting of the histopathology, institutional practice, and patient preference bound to make important impact on the adjuvant treatment plan and outcome. In addition, most of the publications do not furnish much details of the salvage treatment which has an important role in such situation. The present analysis revealed a modest median PFS of

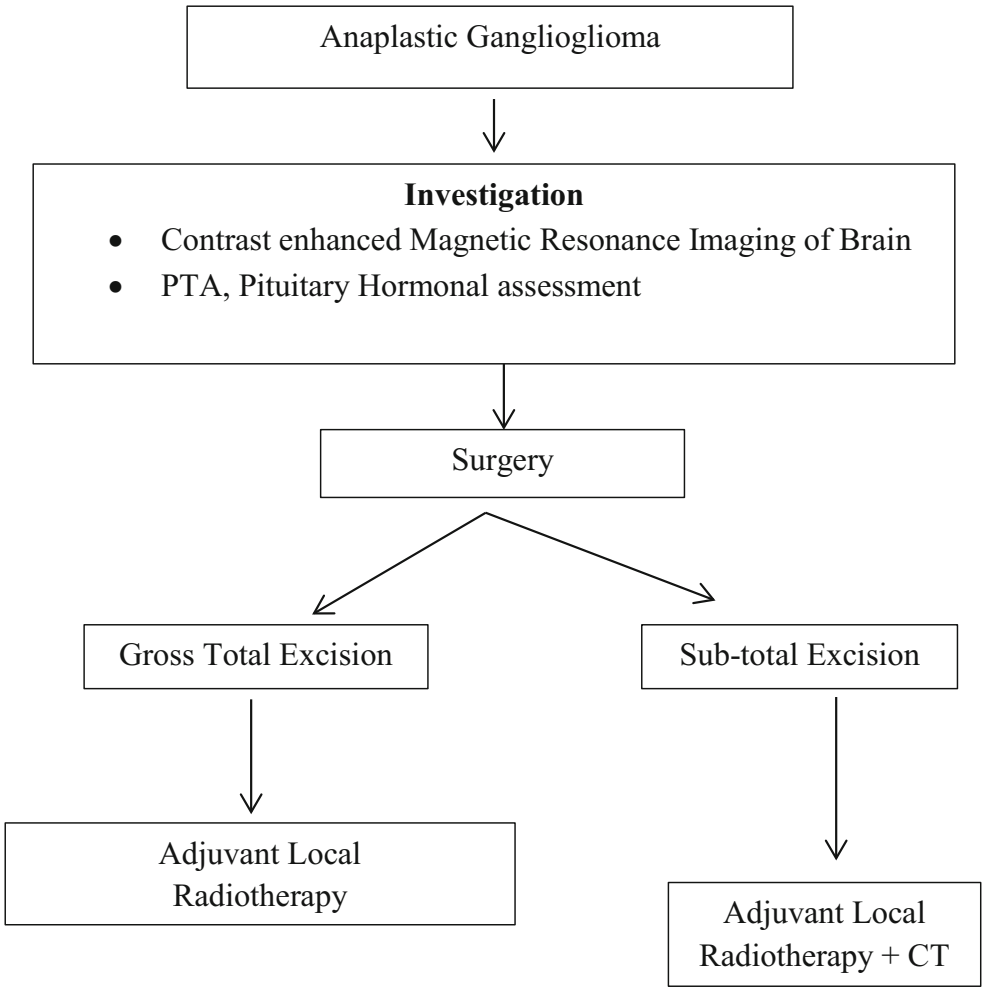

Fig. 4 A suggested treatment algorithm for AGG

24 months [95% CI 9.7–38.2 months] and OS of 29 months [95% CI 15.8–42.2 months]. The survival outcomes are absolutely not different from the observation made by Selvanathan et al. and Terrier et al. depicting importance of more aggressive course of adjuvant therapy for these patients [3, 4]. Though the analysis failed to find an advantage of adjuvant radiation or chemotherapy, it appears reasonable to advocate at least radiation for those who had a GTR and adjuvant radiation and chemotherapy both for those with a STR or in disease at eloquent location [Fig. 4].

This analysis has many limitations. All the publications included in the analysis are retrospective that brings into question various sources of bias. All relevant data was not available which compelled analysis in limited samples for different parameters. But with such rare diseases like AGGs, it is difficult to get better quality data than this and a randomized controlled trial is not reasonable. The use of individual patient characteristics for analysis may be considered as one of the merits of this work.

Conclusion

AGG is associated with a dismal outcome with a median progression-free survival of 24 months and median overall survival of 29 months. Pediatric patients and patients with a gross total resection of tumor had a better PFS and OS. The role of adjuvant therapy remains unclear because of heterogeneity of practice and small patient number. Hence, a gross total resection should remain the aim of surgery, and adjuvant radiation and chemotherapy should be employed to improve the outcome of these patients. An across institutional pooling of data and detailed molecular analysis will further refine the treatment recommendation and survival.

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