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Impact of gross-total resection versus other extent of resections for the overall survival of anaplastic astrocytoma. A systematic literature review

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Keywords
anaplastic astrocytoma, gross total resection, subtotal resection, overall survival

Abstract

Aim: We aim to assess the overall survival (OS) in patients with Anaplastic Astrocytoma (AA) undergoing gross total resection (GTR) as compared to partial resection (PR) subtotal resection (STR), or biopsy.

Methods: This systematic review followed Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines. An electronic search from PubMed/Medline was conducted from their inception to 26th April 2022. We included AA patients undergoing any surgical intervention resulting in GTR, PR, STR or biopsy. We did not include letters, case reports, abstracts, conference papers, reviews, and studies where full text was unavailable. We included only those articles which were published in English.

Results: Five cohorts were used in this study. Two studies assessed OS in GTR, PR/STR and biopsy, while one study compared GTR and STR/biopsy. Another study was used to compare OS between GTR and local excision/STR, and another was used to assess the complications/benefits of these surgeries. Three studies showed a significant increase in OS in patients who underwent GTR compared to the other interventions, while one study showed a non-significant effect on OS (p= 0.249).

Conclusion: Our study concluded a significant increase in OS when patients with AA had GTR instead of STR, PR or biopsy. Although these surgeries might carry some disadvantages, GTR allows a more positive effect on neurological status. Still, more studies need to be conducted to assess the efficiency of these surgeries.

Introduction

Anaplastic Astrocytoma (AA) is a malignant primary brain tumor originating from astrocytic cells, with an annual incidence of 14 per 100,000 person-years [1]. AA is classified as a rapidly infiltrating WHO grade III tumor with increased cellularity, nuclear atypia, marked mitotic activity, presence of GFAP markers, and no microvascular proliferation

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[2]. AA is associated with mutations of TP53, ATRX, and isocitrate dehydrogenase enzymes (IDH1 and IDH 2) [3]. IDH is a key metabolic enzyme in Kreb's cycle that catalyzes the conversion of isocitrate to α-ketoglutarate. Parenteral astrocytoma, endometrial cancer, and melanoma are risk factors for AA [4]. AA presents at a mean of 41 years of age with clinical symptoms including focal seizures, generalized seizures, progressive cognitive deterioration, headache, and blurred vision [5]. The gold standard for diagnosis of AA is a brain MRI which shows a hypointense lesion on T1-weighted images and a hyperintense lesion on T2-weighted images [6].

AA has a better prognosis and overall mean survival than grade IV glioblastoma. Favorable factors for a better prognosis include younger age (<50 years), peripherally located tumor in an accessible area, and intact neurological function [7]. In a study comparing prognostic markers in grade III gliomas, the median survival for patients <40 years was about 65.5 months, and 4.4 months for patients >60 years of age [8]. Tortosa et al. assessed clinical, and radiological factors with prognostic value in anaplastic gliomas. Factors associated with increased survival were age <49 years ($P < 0.03$), postoperative KPS score >80 ($P < 0.007$), and no ring enhancement ($p = 0.03$) [9].

The extent of tumor resection has improved survival in glioma patients. Gross total rection (GTR) and Subtotal resection (STR) are the surgical options for AA patients. Tortosa et al. found no improvement in survival when comparing GTR, STR, and biopsy in anaplastic glioma patients [9]. Another study compared biopsy with resection of the tumor in improving survival in malignant glioma patients. Analysis showed a significantly higher survival ($p = 0.0015$) in patients treated with resection, even after excluding patients with age >65 years or KPS <70 to eliminate the possible risk of bias [10]. Vuorinen et al. found significantly longer survival (171 vs 85 days, $p = 0.035$) in malignant glioma while comparing resection of the tumor and radiotherapy with biopsy and radiotherapy [11].

No review has assessed the role of the extent of surgical resection in improving overall survival in AA patients. Therefore, this review aims to compare GTR with any other partial surgical resection in improving overall survival in grade III AA patients

Method

1. Data sources and search strategy

This systematic review followed Preferred Reporting Items for Systematic Review and Meta analyses (PRISMA) guidelines [12]. An electronic search from PubMed/Medline was conducted from their inception to 26th April 2022 using the search string: (Astrocytoma OR grade III astrocytoma OR grade 3 astrocytoma OR Anaplastic Astrocytoma OR grade III glioma OR high-grade glioma) AND (Gross total resection OR subtotal OR partial resection) AND (extent). Furthermore, we manually screened the cited articles from previous meta-analyses, systematic review, cohort studies including retrospective or prospective studies, and other review articles to identify any suitable studies.

2. Study selection

All studies were included if they met the following eligibility criteria: which can be given as PECOS: 1) P (Population): Patients with Anaplastic Astrocytoma (Grade III tumor); 2) I (Intervention): Gross total resection; 3) C (Control): partial surgical resection intervention; 4) O (Outcome): relative overall survival between the Gross total resection vs any other partial surgical resection intervention 5) S (Studies): Randomized Controlled Trials and Cohort studies published in English.

3. Data extraction and quality assessment of studies

Two reviewers independently searched electronic databases. Studies searched were exported to the EndNote Reference Library software version 20.0.1 **(**Clarivate Analytics**),** and duplicates were screened and removed.

Three reviewers did data extraction and quality assessment of included studies simultaneously and independently. Newcastle-Ottawa Scale (NOS) was used to assess the quality of the cohort studies. NOS score <6 was considered high risk for bias, 6-7 was moderate, and a score >7 was considered a low risk of bias (Table 1).

4. Statistical analysis

The results were formed by using a qualitative analysis. We intended to summarize the findings of the articles to synthesise the results. It was selected as it incorporated the results from all articles and highlighted all the differences and similarities

between the study findings. However, since the included studies showed heterogeneity among their evaluation criteria and results, with not all studies containing appropriate findings to carry out a meta-analysis, we decided to do a systematic review instead.

Results

1. Literature search results

The initial search of the three electronic databases yielded 860 potential studies. After exclusions based on titles and abstracts, the full texts of 136 studies were read for possible inclusion. A total of 5 studies remained for qualitative analysis. Figure 1 summarizes the results of our literature search.

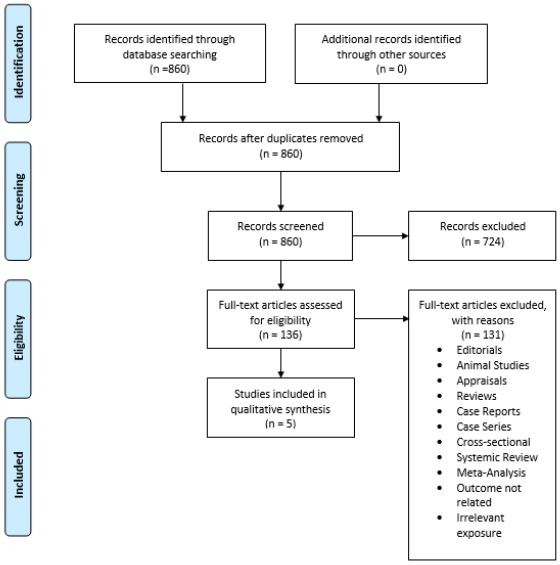

Figure 1. Prisma Flow Chart

2. Study characteristics

Table 2 provides the basic characteristics of included studies. All studies were cohort. We included 2,932 patients in our study. Mean percentage of females in our study was 43.5%. Three studies were from USA and one from Spain and another one from Germany. Mean age was 39.49 years. Further details of each study are provided in Table 1.

3. Quality assessment

All studies had a Low Risk of Bias (Table 1).

4. Result of qualitative analysis

We included five studies to assess the overall survival (OS) in patients, with Anaplastic Astrocytoma, when they underwent gross total resection (GTR) as compared to partial resection (PR) or subtotal resection (STR) or biopsy [13-17]. Nagy et al. and Capellades et al. assessed OS in GTR, PR/STR [13,16], and biopsy while McCrea et al. reported a comparison between GTR and STR/biopsy [14]. Padwal et al. compared OS between GTR and local excision/STR [15]. We included Groshev et al. to describe the complications/benefits of these surgeries [16].

Nagy et al. described OS in 2, 3 and 5 years with GTR giving 42% survival chance in 5 years compared to 29% and 9% 5 years survival in STR and biopsy, respectively [13]. Similarly, Padwal et al. reported a statistically significant increase in OS who had GTR instead of local excision/STR ($p < 0.0001$) [15]. McCrea et al also showed significant 2 years OS in Anaplastic Astrocytoma patients who underwent GTR rather than biopsy [14]. However, Capellades et al showed a statistically non-significant median OS chance between the three surgeries ($p = 0.249$) [16].

Groshev et al reported positive and negative outcomes of doing these surgeries. Neurological status was markedly improved in the patients, and seizures also ended after the surgery. However, few cases were seen where a transient motor weakness was resolved later. In addition, no cases of permanent speech impairment were recorded [17].

Discussion

In this systematic review, we assess the effectiveness of GTR in comparison to partial resection in patients with grade III AA. The evidence from four studies suggested significantly better survival in the GTR group than the PR group. Groshev et al. highlighted the neurological outcomes in both groups. GTR group was associated with better neurological status; however, transient motor weakness was observed.

Neurological resection is the standard treatment approach for WHO grade III AA, followed by postoperative radiation therapy [18]. However, resection alone is considered the most effective treatment approach [19]. In 2016, Brown et al. evaluated the association of the extent of resection with survival in glioblastoma. The meta-analysis results showed a significant decrease in mortality at 1-year and 2-year in GTR compared to subtotal resection and biopsy [20]. Another systematic review and meta-analysis compared the GTR with

supratotal resections in glioblastoma multiforme, suggested a median improvement of 10.5 months in supratotal resection, and showed a statistically significant 35% lower risk of mortality with supratotal resection than GTR. However, the study results were restricted by the clinical and methodological heterogeneity among the included articles [21]. Bond et al. found GTR as a superior technique to subtotal resection in adult pilocytic astrocytoma. In our literature search, no previously published meta-analysis or systematic review evaluated the OS and neurological outcome in patients with grade III AA who underwent GTR or STR [22].

Table 1. Quality assessment of cohorts

Study	Selection (Maximum 4)				Comparability (Maximum 2)	Outcome (Maximum 3)			Total score
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	
Nagy et al., 2009	1	1	1	1	1	1	1	1	8
McCrea et al., 2015	1	1	1	1	2	1	1	1	9
Padwal et al., 2016	1	1	1	1	2	1	1	1	9
Capellades et al., 2017	1	1	1	1	2	1	1	1	9
Groshev et al., 2017	1	1	1	1	1	1	1	1	8

Table 2. Baseline demographic characteristics

Study name	Year	Study type	Country	Duration	Number of patients (n)	Female (%)	Mean age (years)	Type of surgery	Net Risk of Bias	Other notes
Nagy et al.	2009	Cohort	Germany	Jan 1988-Jan 2007	104	45	42	Biopsy, Subtotal Resection, and Gross Total Resection	Low Risk	Median overall survival was 32 months after gross total resection, 36 months after subtotal resection, and 12 months after biopsy. Radiotherapy improved overall survival in grade III gliomas
McCrea et al.	2015	Cohort	USA	1988-2010	22	44	10.5	Biopsy, Subtotal Resection, and Gross	Low Risk	Patients treated with Gross total resection had a median overall survival of 3.4

								Total Resection		years, 1.6 years with subtotal resection, and 1.3 years with a biopsy. Females had a better overall survival
Padwal et al.	2016	Cohort	USA	1999-2010	2755	44.36	49.6	Biopsy, Subtotal Resection, Gross Total Resection, and no surgery	Low Risk	The median survival for patients who underwent gross total resection and subtotal resection was 64 and 24 months, respectively. Patients, less than 50 years of age had better survival
Capellades et al.	2017	Cohort	Spain	2005-2014	37	43.2	N/A*	Biopsy, Subtotal Resection, and Gross Total Resection	Low Risk	Among stage III patients, there was no significant difference in overall survival when resection was attempted (P=0.1). The statistical power may not have been sufficient to detect a difference with only 37 patients.
Groshev et al.	2017	Cohort	USA	Sep 2012-Feb 2015	14	41	55.86	Subtotal Resection, Near-total Resection, and Gross Total Resection	Low Risk	93% of patients had either gross total or near-gross total, which represents a favorable extent of resection. The extent of resection was better than the published outcomes of gross total near-total resection at 91%

N/A*= Not available

Groshev et al. included 18% WHO grade III astrocytoma patients, other resectable tumors; metastasis to the brain, gliomas, WHO grade I, grade II, and grade IV. They reported that GTR was associated with neurological status, including motor and sensory deficits improvement. Overall, 5 of 76 patients developed transient motor weakness, and one developed a transient speech deficit; however,

deficits were resolved within two months postoperatively [17]. McCrea et al. found a median OS of 3.4 years in the GTR group compared to the median 1.6 years OS in STR and 1.3 years in the biopsy group. In addition, they found significantly longer OS in the female patient (8.1 years) in comparison to male patients (2.4 years). However, the OS was also significantly correlated with tumor location [14]. Similar results were reported by Padwal et al., they found a significant correlation between OS and extent of resection [15]. Nagy et al. found that median OS was 32 months after GTR, 36 months after STR, and 12 months after biopsy in grade III AA [13].

The results of the quantitative analysis suggested improvement in the OS in GTR; however, due to the heterogeneity among the results of included studies, strong results could not be predicted. In addition, only one study highlighted the postsurgical neurological outcomes. Therefore, more extensive trials and prolonged follow-ups are needed to evaluate OS associated with GTR and STR in grade III AA.

Limitations

Our study was limited by the following factors: (a) few articles were included in our manuscript; (b) only cohorts were included; (c) only one article discussed issues in the surgeries but was also not clear on which grade was more affected. However, these articles were pivotal in doing this review.

Conclusions

Our study concluded a significant increase in OS when patients with AA had GTR instead of STR, PR or biopsy. Although these surgeries might carry some disadvantages, GTR allows a more positive effect on neurological status. Still, more studies need to be conducted to assess the efficiency of these surgeries.

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