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The impact of extent of resection on the long-term surgical outcome of grade II diffuse astrocytoma: a retrospective study

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Abstract. ***Background.*** *Diffuse astrocytomas (DAs) are slow-growing, primary, diffuse brain tumors that originate from glial cells. As part of low-grade glioma, grade II DA is a tumor with unclear borders; small clusters of tumor cells tend to expand into and infiltrate adjacent healthy tissue. Major debate surrounds the predictive value of the extent of resection (EOR) in DA. To evaluate the impact of the EOR on the surgical outcomes in grade II DA over the long-term, we conducted a retrospective analysis. Specifically, we aimed to evaluate the correlation between pre- and postoperative tumor sizes and overall survival (OS).* ***Materials and methods.*** *Patients diagnosed with diffuse astrocytoma between 2010 and 2020 who underwent surgery to remove the tumor and were then monitored until January 2022 were included in our retrospective review. The EOR was determined as preoperative volume minus postoperative volume divided by preoperative volume multiplied by 100 %, and then categorized into five groups based on magnetic resonance imaging obtained 72 hours following surgery. There are five categories: 1) > 99 % — gross total resection; 2) 91–99 % — near-total resection; 3) 70–90 % — subtotal resection; 4) 70 % — partial resection; 5) biopsy. The independent relationship between the EOR and subsequent OS was analyzed using a multivariate proportional hazards regression model.* ***Results.*** *In the end, we included 18 cases in our investigation. All patients had a mean survival of 35.33 months, 38 months in males (n = 12, mean age 40.83 years) and 22 months in females (n = 6, mean age 32 years). We divided the observed patient survival periods into five distinct classes based on the EOR. We found that a higher EOR predicts a better prognosis for adult individuals with diffuse astrocytoma. There was no statistically significant correlation between the pre- or postoperative tumor volume and the OS, as determined by regression analysis.* ***Conclusions.*** *Greater EOR is indicative of a better prognosis for patients with diffuse astrocytoma. Our results provide a much-needed re-evaluation of surgical efficacy in diffuse astrocytoma and support the use of maximal resection as initial treatment. Patient survival does not seem to be related to the size of the removed tumor.*

Keywords: *glioma; diffuse astrocytoma; astrocytoma; extent of resection*

Introduction

Diffuse astrocytomas (DAs) are a kind of low-grade glioma (LGG) with a WHO (World Health Organization) grade II classification. Depending on the source, the average lifespan of a person with DA might be from 3.9 to 10.8 years. Many LGG patients have a good prognosis over the long period, but some undergo anaplastic transition that could cause irreversible brain injury and even death [7–10].

DAs are classed as IDH-mutant, IDH-wildtype, or not otherwise described based on the mutation status of the IDH gene [11]. DAs infiltrate brain parenchyma, however, complete removal is challenging: 14 to 17 % of total gross resections are performed [2, 3]. This means that persistent tumors pose a challenge in the long-term monitoring of DA patients. Young and middle-aged people (age at diagnosis is on average 40 years) are disproportionately affected by DAs,

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despite the fact that they are very rare tumors making up only approximately 15 % of gliomas [12–14].

We did a retrospective study to see how the extent of resection (EOR) affected the long-term outcomes in DA patients who had surgery to remove their tumors. Neurosurgical treatment of DA is controversial. Identifying prognostic factors such as age at diagnosis, gender, symptom onset, persistence, impairment level, Karnofsky performance score, radiological abnormalities, EOR, and subtype can increase quality of life and lifespan [15–18].

The ***goal*** was to find out whether a greater EOR would significantly improve the overall survival (OS), so a retrospective analysis of outcomes in grade II DA was conducted with a focus on surgical therapy and the present therapeutic strategy.

Materials and methods

Uzhhorod Regional Center of Neurosurgery and Neurology cared for 32 patients with DA between 2010 and 2020. We were unable to include 14 patients in our statistical analysis because of lost contact, missing records, or age under 18. Eighteen patients' medical records were examined retrospectively. Twelve men (66.67 %) with a mean age of 40.83 years and 6 women (33.33 %) with a mean age of 32 years were included in our study. These patients met inclusion criteria, thus, their data were used in the final analysis. At our clinic, we operated adults diagnosed with diffuse astrocytoma (histopathological grade II astrocytoma). As of January 2022, they were still being monitored for results. Only patients with complete clinical data were recorded. This included data of patients, a clinical findings background, imaging results, surgical details, tumor characteristics, and pathology reports.

Diagnosis and follow-up

All patients had headaches and neurological impairments. All these individuals underwent preoperative magnetic resonance imaging (MRI) with and without gadolinium, MRI was also performed within 72 hours after surgery. Patients were followed for 2 to 144 months (median 36 months) after hospital discharge. Follow-up MRIs were serial in all patients. Data on postoperative quality of life and recurrence was gathered by telephone interviews or examination findings and imaging. T1-weighted MRI revealed the abnormal growth, and a biopsy taken during excision provided conclusive proof of the diagnosis. Preoperative T1 contrast-enhanced MRI was used to evaluate tumor volume. T1 contrast-enhanced images were acquired in an axial (A), sagittal (B), and coronal (C) plane to calculate the tumor volume. We used the same volumetric approach to collect a second MRI image (postoperative) within 72 hours. Follow-up MRIs for recurrence, clinical symptoms, and death were performed until January 2022. All the mortalities were double-checked by family members, phone calls, and messages.

Data management and analysis

Preoperative tumor volume (X) was classified into four categories: 1) > 20 cm^3; 2) 20–50 cm^3; 3) 51–100 cm^3; 4) > 100 cm^3, whereas postoperative tumor volume (Y) had three categories: 1) 0.1–10 cm^3; 2) 10.1–50 cm^3; 3) 50.1–100 cm^3. The EOR was calculated by subtracting the volume before and after surgery and multiplying the result by 100 %. Using the newly obtained EOR, we categorized our information as follows: 1) gross total resection (GTR); 2) near total resection (NTR); 3) subtotal resection (STR); 4) partial resection (PR), and 5) biopsy for rates of 70 %. Our key finding was an increase in postoperative survival time. Time of survival

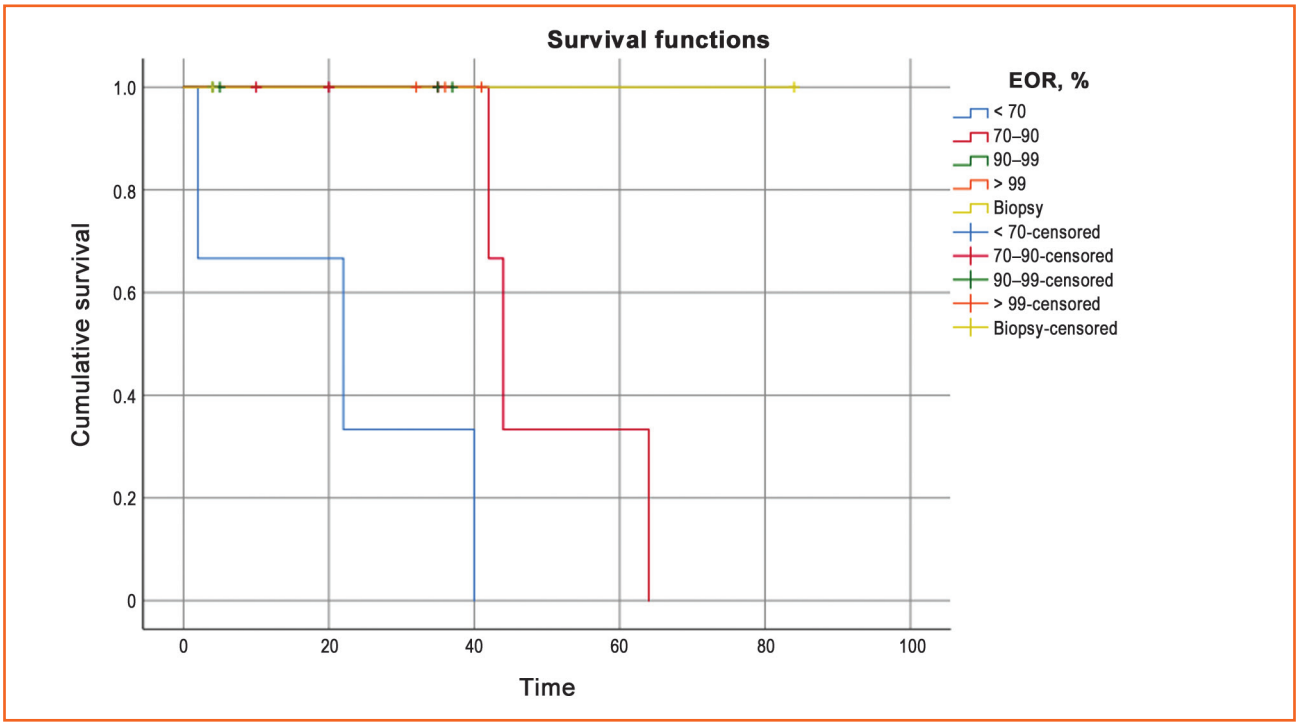

Figure 1. Kaplan-Meier survival graph with the EOR as factor variable

was measured in months after surgery (and was stratified by the EOR). A log-rank test was used to determine the effect of the EOR on survival. Furthermore, Cox regression analysis models were used to determine the impact of pre- and postoperative volumes on the median survival time.

Results

Our ultimate sample size was 18 patients (12 men and 6 women), after evaluating 32 initial records. The average age of a male patient at diagnosis was 40.83 years. At the end of the observation period, 7 males (58.33%) were still alive, mortality rate was 41.66 %. Males had a significantly lower OS at 32 months on average, with only two cases of recurrence. For women, the average age at diagnosis was 32 years. Five females were still alive by the end of the follow-up period (16.66 %). There was only one recurrence in women, and their median OS was 22 months.

Survival analysis (Kaplan-Meier method)

Kaplan-Meier method with log-ranking was used to assess the survival rate for the EOR percentage as a factor variable. Time was calculated in months (Fig. 1).

The results of log-rank test showed that there is a significant difference in time of death from operation date for the EOR percentage (Table 1). The longest survival time since surgery for respondents in < 70 % EOR group was 40 months. On the other hand, the longest survival time for respondents in 70–90 % EOR was 64 months after intervention. The censored category in the graph shows respondents who were alive at the time of recording data. It indicates that all the respondents in 90–99 % EOR, > 99 % EOR were alive at the time of data recording and there were no deaths in this category. Log-rank test was significant (χ^2 (4) = 16.255, $p < 0.01$), which shows that there is a significant difference in survival curves between people in different categories of the EOR variable. However, the sample size of 18 was very low to reach any conclusion and the results don't mean anything as a lot of assumptions are not being met. A sample size of at least 100 would have made the results more meaningful.

Cox regression with preoperative tumor

Omnibus test was not significant ($p = 0.456$) (Table 2). Therefore, there was no impact of preoperative tumor on survival.

First category of preoperative volume (i.e., < 20 cm^3) was used as reference and the results indicate there is no difference in survival and hazard rates of other two preoperative categories compared to the first one ($p > 0.05$) (Table 3). Preoperative volume of 51–100 cm^3 had a very high hazard ratio of 4.147. However, it was not statistically significant.

Cox regression with postoperative volume

Omnibus test was found to be significant (χ^2 (2) = 6.394, $p < 0.05$) (Table 4). However, postoperative volume had no impact on survival ($p = 0.146$).

Table 1. Log-rank test for survival based on the EOR

Overall comparisons			
	Chi-Square	df	Sig.
Log-rank (Mantel-Cox)	16.255	4	0.003
Test of equality of survival distributions for the different levels of the EOR percentage			

Table 2. Omnibus test for preoperative tumor

Omnibus tests of model coefficients[a]									
	Overall (score)			Change from previous step			Change from previous block		
–2 log likelihood	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
19.121	1.818	2	0.403	1.569	2	0.456	1.569	2	0.456

Note: here and in Table 4: [a] — beginning block number 1. Method = Enter.

Table 3. Beta coefficient for preoperative tumor

Variables in the equation								
	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI for Exp (B)	
							Lower	Upper
Preoperative volume			1.615	2	0.446			
Preoperative volume (1)	0.371	1.009	0.136	1	0.713	1.450	0.201	10.471
Preoperative volume (2)	1.422	1.134	1.572	1	0.210	4.147	0.449	38.311

As shown in Table 5, there is no difference in survival based on the postoperative volume ($p > 0.05$). A very small sample was chosen, which makes the analysis just a waste of time and we did not achieve anything as no assumptions are going to be met in a sample size of 18 respondents only with only six being at risk.

Discussion

We found that the greatest EOR was associated with a longer overall survival. In comparison to earlier studies that revealed GTR rates ranging from 4 to 15 % [19–21], ours was greater because we prioritized attaining the maximum surgical resection possible for each patient.

According to Smith et al. [22], patients with greater than 90% resection had five- and eight-year OS rates of 97 and 91 %, while those with less than 90% resection had 76 and 60 %. A reduced postoperative tumor volume is linked to a longer OS, but Mariani et al. [23] achieved > 90% excision in only 10 % of patients. Because tumor volume correlates with poor prognosis, surgical excision is recommended before tumor begins to grow. In our analysis, the median time to death for those with the EOR of 70 % or less was 40 months after surgery. On the other hand, patients with the EOR between 70 and 90 % had a median survival of 64 months. In any of the other subgroups, the EOR factor did not play a role in anyone's death. At the time the data was obtained, there were no fatal cases occurring among individuals who had the EOR of 90 % or higher or greater than 99 %. According to our findings on the tumor volume, the preoperative volume ranging from 51–100 cm^3 was associated with a risk ratio that was 4.147 times greater for overall survival. Although postoperative volume did not affect survival, the difference was not statistically significant ($p = 0.146$).

For this reason, tumors are strongly advised to be surgically excised before their volumes increase and prognosis worsens. Due to the small tumor volume, which was statistically related with a longer OS in the univariate analysis, 76.67 % of patients in our study underwent a gross total resection. The question of when surgery is most beneficial for individuals with low-grade infiltrative gliomas is still highly contested [8, 17, 24–27]. Compared to debulking therapy alone, we show that a more extensive resection does predict considerably improved OS. As we get closer to the limits of the EOR in total resection, we expect survival rates to improve dramatically. Expected survival time is drastically altered by even a little quantity of residual tumor.

Smaller lesions may have a different biology than larger ones, according to research [23, 28, 29]. Greater pretreatment tumor volume was related to shorter OS. We identified a 4.147 overall survival risk ratio among DA patients with tumor sizes between 51 and 100 cm^3. Larger tumors may have a faster growth rate, resulting in a faster recurrence after a gross total resection or a quicker rate of growth following a partial resection. Patients with larger tumors before surgery may have a shorter OS due to a quicker growth rate. Inconsistent EOR definitions from previous research impede accurate comparisons of patient outcomes. Three of the five papers on the EOR in LGGs that met basic design requirements were reviewed by Keles et al. [25]. The 5- and 8-year OS rates in the present dataset are much higher than those of Soffietti et al. [30]. Postoperative survival for patients who underwent partial resection was 40 months. STR resulted in a 64-month post-surgery survival rate. The graph's censored group represents patients who had not died yet. This means no NTR or GTR respondents died before data collection.

Although Wijnenga et al. [21] recently evaluated the impact of surgery in a large cohort of molecularly defined grade II diffuse gliomas and found that larger postoperative glioma volume was associated with worse overall survival (risk ratio 1.01 per 1 cm^3 increase in residual glioma volume), Wahl et al. [31] investigated postoperative tumor volume and DA survival. This finding supports maximal safe resection in all

Table 4. Omnibus test for postoperative tumor

Omnibus tests of model coefficients[a]									
	Overall (score)			Change from previous step			Change from previous block		
–2 log likelihood	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
15.441	6.394	2	0.041	5.250	2	0.072	5.250	2	0.072

Table 5. Coefficients for postoperative tumor

Variables in the equation								
	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI for Exp (B)	
							Lower	Upper
Preoperative volume			3.851	2	0.146			
Preoperative volume (1)	8.236	177.613	0.002	1	0.963	3772.615	0.000	5.765E+154
Preoperative volume (2)	10.518	177.611	0.004	1	0.953	36987.919	0.000	5.635E+155

LGG subtypes. In IDH-mutant astrocytoma, even minute tumor remnants affect OS. The survival difference between 0.1–5.0 and 0.0 cm^3 tumor remains significant. The EOR is a prognostic indication for DA patients. The higher EOR improves overall, progression-free survival, and time to malignant transformation [32]. Maximizing the EOR and preventing neurological deficits are the goals of surgery. Innovative surgical procedures [33] are used for the safest resections. Our analysis shows that all NTR and GTR respondents were alive at the time of data collection.

Conclusions

Survival rates of patients with diffuse astrocytoma are influenced in multiple ways by the degree of surgical resection. Significantly more surgical resection is advantageous for patients with DA. We found no difference in survival rates between smaller and larger tumor volumes. The grade II DAs require additional research with bigger cohort sizes and molecular substratification.

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Вплив обсягу резекції на віддалені хірургічні результати при дифузній астроцитомі II ступеня: ретроспективне дослідження

Анотація. ***Актуальність.*** Дифузні астроцитоми (ДА) — це повільно зростаючі первинні дифузні пухлини головного мозку, що походять з гліальних клітин. У складі гліоми низького ступеня злоякісності ДА II ступеня є пухлиною з нечіткими межами; невеликі скупчення пухлинних клітин мають тенденцію поширюватися в прилеглі здорові тканини та проникати в них. Основні дебати точаться навколо прогностичного значення обсягу резекції (ОР) при ДА. Щоб оцінити вплив ОР на результати хірургічного втручання при ДА II ступеня в довгостроковій перспективі, ми провели ретроспективний аналіз. Зокрема, ***метою*** було оцінити кореляцію між до- та післяопераційними розмірами пухлини та загальною виживаністю (ЗВ). ***Матеріали та методи.*** Пацієнти з діагнозом дифузної астроцитоми, установленим між 2010 і 2020 роками, які перенесли операцію з видалення пухлини, а потім знаходилися під спостереженням до січня 2022 року, були включені в наш ретроспективний огляд. ОР визначали як передопераційний об'єм мінус післяопераційний об'єм, поділений на передопераційний об'єм, помножений на 100 %, а потім класифікували в п'ять груп на основі результатів магнітно-резонансної томографії, отриманих через 72 години після втручання. Існує п'ять категорій: 1) > 99 % — тотальна резекція; 2) 91–99 % — майже тотальна резекція; 3) 70–90 % — субтотальна резекція; 4) 70 % — часткова резекція; 5) біопсія. Незалежний зв'язок між ОР та наступною ЗВ аналізували за допомогою багатовимірної регресійної моделі пропорційних ризиків. ***Результати.*** Зрештою, ми включили до нашого дослідження 18 випадків. Усі пацієнти мали середню виживаність 35,33 місяця: 38 місяців у чоловіків (n = 12, середній вік 40,83 року) і 22 місяці в жінок (n = 6, середній вік 32 роки). Ми розділили спостережувані періоди виживання пацієнтів на п'ять різних класів на основі ОР. Виявлено, що вищий показник ОР передбачає кращий прогноз у дорослих осіб із дифузною астроцитомою. Не було статистично значущої кореляції між до- або післяопераційним об'ємом пухлини та ЗВ, як визначено регресійним аналізом. ***Висновки.*** Вищий показник ОР вказує на кращий прогноз у пацієнтів із дифузною астроцитомою. Наші результати підтверджують необхідність переоцінки хірургічної ефективності при дифузній астроцитомі та підтримують використання максимальної резекції як початкового методу лікування. Виживаність пацієнтів, напевно, не залежить від розміру видаленої пухлини.

Ключові слова: гліома; дифузна астроцитома; астроцитома; обсяг резекції