

THERAPEUTIC OPTIONS AND PROGNOSTIC FACTORS IN TREATMENT OF ANAPLASTIC GLIOMAS

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Received: 07.06.2021.

Accepted: 10.09.2021.

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ABSTRACT

Anaplastic gliomas compromise about 5.9% of primary CNS tumors. The main goal of the operation is the maximum removal of the tumor, reduction of the tumor mass and reduction of the increased intracranial pressure. Different pathohistological subtypes of anaplastic gliomas show significantly different prognosis depending on the applied oncological therapeutic protocol as well as the modality of the applied radiotherapy. The study was designed as a retrospective, clinical observational study. The study included 34 participants who were diagnosed with anaplastic glioma in the followed time period. Survival rates were calculated based on the localization, modality of therapy and complications. We concluded that 20,4% of anaplastic gliomas were formed by transformation from previously operated lower grade gliomas. The initial sign of the disease is the appearance of epileptic seizures. Anaplastic gliomas most oftenly occur in the frontal region, with a frequency of 47%. The incidence of anaplastic gliomas in the temporal lobe is 23,5%. The length of survival is in relation to the localization of tumor expansion($p<0.05$). The overall survival in the group of anaplastic gliomas operated on in the Department of Neurooncology KCS in the follow-up period of five years is 52.9%. The application of different chemotherapy modalities is not significant predictor in the length of survival. The radical nature of the operation has significance in the length of patient survival, which confirms the conclusions of most of the conducted studies cited in oncology textbooks.

Keywords: Anaplastic glioma, surgical treatment, survival rate, neurooncology.



UDK: 616.831-006

Eabr 2024; 25(3):219-224

DOI: 10.2478/sjecr-2021-0043

INTRODUCTION

Classification and treatment of anaplastic gliomas (WHO gr III) is the subject of numerous debates and discrepancies in the field of neurooncology. [1] The incidence and prevalence of brain tumors has been inaccurately documented for a long period of time, no benign tumors or metastatic diseases were reported before the beginning of 2003. A database from the U.S. Central Brain Tumor Registry from 2006 to 2010 indicates that the incidence of brain tumors in children aged 0 to 19 was 5.26 per 100,000, and 27.38 per 100,000 for adults. [2] Secondary brain tumors are, depending on the literature data, three to ten times more common than primary tumors. The classification of brain tumors lists about one hundred subtypes of CNS malignancies. As testing for genetic disorders is routinely used in diagnostic procedures for gliomas, clinicians and pathologists also encounter certain practical problems, such as conflicting outcomes due to different interpretations of genetic alterations, this segment may be a somewhat variable part of diagnostic data. Within the classification in which "genotype dominates over phenotype", the accuracy of molecular tests is crucial, which requires adequate knowledge of the pathologist.[3] Gliomas account for 80% of primary malignant brain tumors [4] The group of anaplastic gliomas includes astrocytomas, oligodendrogliomas, oligoastrocytomas, pleomorphic xanthoastrocytomas. Anaplastic gliomas compromise about 5.9% of primary CNS tumors. [5]

Therapy involves multimodal therapy that includes maximal surgical reduction, followed by chemotherapy and radiotherapy. The main goal of the operation is the maximum removal of the tumor, reduction of the tumor mass and reduction of the increased intracranial pressure, as well as providing the tissue for pathological analysis in a way that minimizes the risk of neurological deficit. Anaplastic gliomas are infiltrative tumors, which makes complete surgical resection virtually impossible. Nevertheless, the operation achieves the effect of reducing the mass effect, edema and the potential for development of hydrocephalus. Retrospective evidence from the literature indicates that better treatment outcomes are associated with radical surgery, because cells that are out of the cell cycle and thus resistant to chemotherapy and radiotherapy are removed. Cytoreduction initiates the proliferation of G0 tumor cells into a more vulnerable phase of the cell cycle. Technological advances in surgical approaches, techniques, and instrumentation have made most tumors available for resection. [2] Different pathohistological subtypes of anaplastic gliomas show significantly different prognosis depending on the applied oncological therapeutic protocol as well as the modality of the applied radiotherapy. The median survival after surgery for anaplastic astrocytoma is about 19 months Survival estimates for these tumors vary widely and seem to be associated with age,[6,7] Karnofsky Performance Score (KPS) status,[8,9] extent of surgical resection,[10] use of adjuvant radiotherapy,[11] ki-67 immunohistochemical markers,[12-14] and sensitivity to chemotherapy as determined by genetic mutations such as

IDH1(Isocitrate dehydrogenase 1) [15], PTEN, EGFR amplification,[16] and 1p19q codeletion.[17].

MATERIALS AND METHODS

Study design

The study was designed as a retrospective, clinical observational study. The study used clinical and diagnostic data from the patients that were treated surgically in the Clinic for neurosurgery of Clinical center of Serbia diagnosed with brain tumors that after PH verification confirmed to be anaplastic gliomas. Clinical data were collected retrospectively, by reviewing medical histories and conciliatory decisions recorded in an electronic database, and then analyzed prospectively. All data were obtained from period of 2011 to 2014.

Examined variables:

The study included data on demographic and socio-economic parameters, personal and family history, localization, pathohistological subtype of tumor and applied oncological protocol.

Pathohistological analysis was performed at the Clinic for Neurosurgery KCS, using standard hematoxylin-eosin staining, as well as immunohistological staining.

Research instruments:

- Preoperative CT and MR of the endocranium
- Postoperative CT of the endocranium used to determine the degree of tumor resection.
- Periodic control MRI of the endocranium used to determine the success of applied chemotherapy and radiotherapy.
- ECOG PS(Eastern Cooperative Oncology Group Performance Score) and Karnofsky performance score

Statistical data processing

Data processing was performed in SPSS Windows 20.0. All data are presented and analyzed by adequate mathematical and statistical methods appropriate to the type and type of data, the results will be presented in tables and graphs. For normal variables, mean and standard deviations were calculated. P-values less than 0.05 were considered statistically significant.

RESULTS

The study included 34 patients diagnosed with anaplastic gliomas that were treated in at the Department of Neurooncology. In the group of patients with anaplastic gliomas there were 15(44%) patients with anaplastic astrocytoma, 9(27%) patients with anaplastic oligodendroglioma and 10(29%) patients with anaplastic oligoastrocytoma. Patients whose pathohistological diagnosis would confirm the finding of

anaplastic pleomorphic xanthoastrocytoma were not operated on in the monitored period.

The age median was 43 years. The youngest patient who underwent surgery was 23 years old, while the oldest patient was 63 years old. Of the total number of operated patients, 26(76.5%) of patients were female, 8(23.5%) were male.

By analyzing the data on previous hospitalizations and previously applied surgical treatment, as well as insight into pathohistological findings obtained in previous operations we concluded that 20,4% of anaplastic gliomas were formed by transformation from previously operated lower grade gliomas.

The initial, dominant sign of the disease is the appearance of epileptic seizures, followed by signs of elevated ICP(intracranial pressure), hemiparesis, psychoorganic syndrome, diplopia and other symptoms. The basic sociodemographic and clinical data can be seen in **figure 1**.

Table 1. Basic sociodemographic and clinical data of the patients.

Gender	Male 8(23.5%)
	Female 26(76.5%)
Age	Minimum 23
	maximum 63
	median 43
Anaplastic glioma subtype	astrocytoma-15 (44%)
	oligodendroglioma-9(27%)
	oligoastrocytoma-10(29%)
	xanthoastrocytoma-0(0%)
Classification based on previous existence of gliomas	de novo tumor 79.4%
	previously operated lower grade glioma-20.6%
Dominant symptoms	epileptic seizure 44.1%
	Hemiparesis 11.8%
	signs of elevated ICP 20.6%
	psychoorganic syndrome 8.8%
	diplopia 2.9%
	other symptoms 11.8%

According to the localization of anaplastic gliomas, they most often occurred in the frontal region, with a frequency of 47%. When examining on which side tumors appeared more often, we concluded that more often tumors appear the right side, then on the left side and then on both sides of the frontal region. percentual representation of most common tumor localizations in this study can be seen in **figure 1**.

TUMOR LOCALISATION

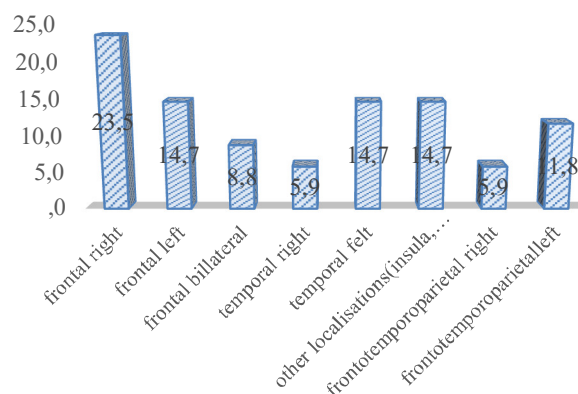


Figure 1: percentual representation of most common tumor localizations in this study.

The incidence of anaplastic gliomas in the temporal lobe is 23.5%. Statistical analysis revealed a statistically significant difference ($p < 0.05$) in the length of survival in relation to the localization of tumor expansion.

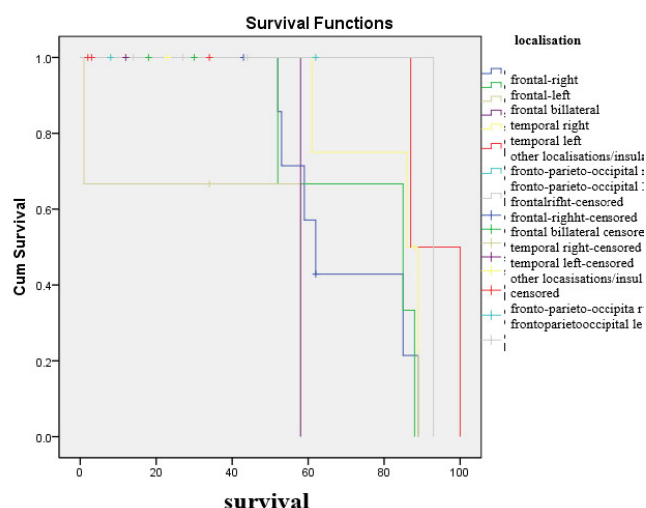


Figure 2. Survival functions in patients with anaplastic gliomas depending of localization.

In over 50% of cases, tumor extirpation was achieved intraoperatively, based on data from operative lists and discharge letters, as well as postoperative computed tomography, in the early postoperative period. Intraoperative subtotal reduction was achieved in 32% of cases. In the group of operated patients with anaplastic gliomas, early postoperative complications were verified in 14 patients. In 5 patients, bleeding in the operative lodge was observed in the early postoperative course, which was the reason for reoperation. In 3 patients, internal hydrocephalus developed, due to which the cerebrospinal fluid drainage system was placed, in 3 patients, postoperative cerebrospinal fluid was observed at the site of the operative wound, which was resolved by repeated

lumbar punctures. Statistical analysis showed that there was no significant difference in the length of survival in relation to the occurrence of postoperative complications ($p > 0.05$).

Postoperative chemotherapy and radiation therapy were not administered to five patients, due to the Karnofsky score below 60 and the inclusion of symptomatic therapy. In 67.6% of cases, chemotherapy was used as BCNU monotherapy. The combined PCV protocol was applied in 14.7% of cases (Figure 3). Statistical analysis did not determine the significance in the length of survival, in relation to the applied chemotherapy modality. 3D conformal radiotherapy was applied in 85% of cases.

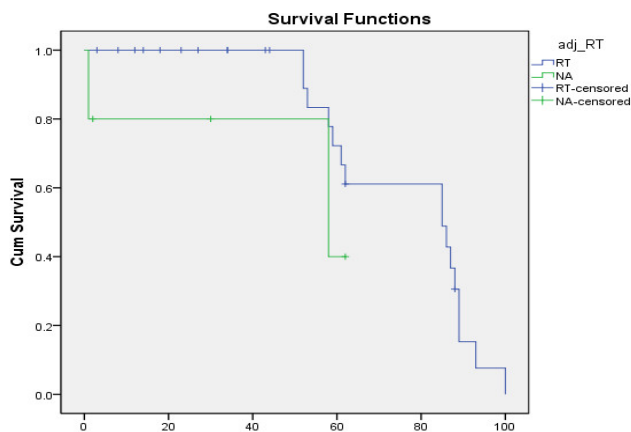


Figure 3. Overall survival in the group of anaplastic gliomas in patients with adjuvant radiotherapy.

The overall survival in the group of anaplastic gliomas operated on in the Department of Neurooncology KCS in the follow-up period of five years is 52.9%. In the group of astrocytomas 80% of patients survive for one year, while the three-year survival is 46.67%. A five-year follow-up resulted in a survival result of 40%.

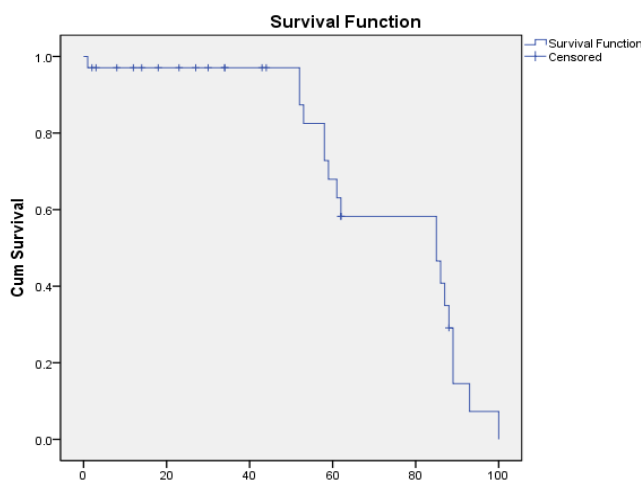


Figure 4. Overall survival in patients with anaplastic gliomas.

In the group of oligodendrogliomas, 88.89% survived the first year after surgery, while the three-year survival in our series is equal to the five-year survival and amounts to 55.56%.

DISCUSSION

Our paper studied the data on patients treated for anaplastic gliomas in the period from October 2011 to December 31, 2014, who were treated at the Clinic for Neurosurgery, Department of Neurooncology. All patients were operated by the same team of neurosurgeons, which contributes to the uniformity of the approach. Decisions on the modality of treatment were made by the Council for CNS Tumors, which consists of a multidisciplinary team of neurosurgeons, medical oncologists, radiation oncologists and pathologists.

According to the literature, the frequency of gliomas in the group of primary brain tumors is 26.4% of all tumors, while the so-called high-grade tumors (grade III and grade IV) make up 19.9% of primary brain tumors. Glioblastoma, according to the US Central Registry, occur with 15.6%, while the incidence of anaplastic gliomas is 4.3%. From this we conclude that about 21.6% of high-grade gliomas are anaplastic gliomas.[2]

According to our results, in a three-year period, in the Department of Neurooncology of the Clinic for Neurosurgery KCS, in the group of operated patients there were 22.7% of patients with anaplastic gliomas, in the group of patients with high - grade gliomas, grades 3 and 4.

In our study, the group of anaplastic astrocytoma makes up 10% of high-grade tumors, while anaplastic oligodendroglioma make up to 6% of high-grade gliomas. According to some published studies, astrocytomas occur with an incidence of 1.7% of primary brain tumors while oligodendrogliomas occur with an incidence of 0.5% of all primary brain tumors. The ratio of astrocytomas and anaplastic oligodendrogliomas in our study is 1.6:1. oligoastrocytoma, NOS (Not Otherwise Specified), is a rare tumor because most high-grade gliomas with mixed or ambiguous histology can be classified as IDH mutated anaplastic astrocyte or IDH mutated anaplastic oligodendroglioma with 1p / 19q correlation [2]. Bearing in mind that in the analyzed period we did not perform, systematically, cytogenetic molecular analyzes, in our work the incidence of anaplastic oligoastrocytomas is identical to the incidence of astrocytomas. histological material is classified in the group of oligoastrocytomas, which is why their incidence in our work is statistically significantly higher than the data from the literature. The results obtained in this study indicate that 76.5% of patients are female, in contrast to studies cited in the literature where 55% of patients with high grade gliomas are male. Until the discovery of the IDH mutation as a molecular marker, the diagnosis of anaplastic glioma was based only on histological evidence.[18] In this era, the peak age was considered to be 45

years of age. In our work, the median occurrence of anaplastic gliomas is 43 years.

The initial symptomatology in terms of the occurrence of EPI seizures is a better prognostic factor, compared to the appearance of other symptoms and signs of the disease. The localization of the tumor in the frontal region has a favorable prognostic significance, which can be associated with the possibility of more radical surgical treatment, as well as more frequent localization of oligodendroglioma in this region. Our study also confirms a statistically significantly worse prognosis in astrocytomas compared to other histological forms of anaplastic gliomas. Proliferative activity, determined with Ki-67 index, is not prognostically significant for astrocytomas. Genetic changes of IDH 1/2 mutations are associated with a better outcome, while IDH wild-type anaplastic astrocytoma has an outcome similar to that of IDH wild-type glioblastoma. (19) EGFR amplification as well as genotype with 7q amplification and 10q deletion were associated with a poorer outcome. Proliferative activity, determined with Ki-67 index, is not prognostically significant for astrocytomas. are not associated with outcome in astrocytoma. Genetic changes of IDH 1/2 mutations are associated with better outcome, whereas IDH wild-type anaplastic astrocytoma has an outcome similar to that of IDH wild-type glioblastoma. EGFR amplification as well as genotype with 7q amplification and 10q deletion are associated with a poorer outcome. By monitoring the impact of surgical complications in the early postoperative course, we do not obtain their statistical significance as a prognostic factor. We seem to explain the seemingly illogical result by the need for continuous monitoring of patients and timely resolution of complications.

Due to the low performance score in 5 patients, no adjuvant radio or chemotherapy was applied. Having that in mind in our study there is no comparison between survival rates in these patients and patients with high performance status and had adjuvant radio and chemotherapy. Other studies showed that patients with Karnofsky Performance Score (KPS) of ≥ 70 have a significantly better 5-year OS (Overall Survival) as compared to those with KPS < 70 (33%). The use of adjuvant temozolomide (TMZ) shows longer 5-year OS compared to 36% in patients who did not receive adjuvant chemotherapy (20)

Unfortunately, we cannot get a general conclusion about the epidemiological characteristics of anaplastic gliomas on the entire territory of the Republic of Serbia, due to the lack of precise unified data. Radical surgery, which is not an end in itself, is one of the basic prognostic factors. In addition to age, general condition, IDH mutational status, and the extent of surgical resection affect the outcome of treatment, which is confirmed by statistical processing of the results obtained in our work. The use of a new generation operating microscope, cavitron ultrasound aspirator, intraoperative navigation and neuromonitoring contribute to the radicality of the operative approach. In that sense, uniform use of the same in all neurosurgical centers in Serbia is necessary. Genetic

changes of the IDH 1/2 mutation are associated with a better outcome, whereas the IDH wild-type anaplastic astrocytoma has an outcome similar to that of the IDH wild-type glioblastoma. [21] In the period we analyzed, and unfortunately not even today, genetic mutations are not systematically examined in all patients operated on for anaplastic gliomas in our country, which is why we cannot compare our results with data from the literature. What is necessary to introduce into routine use in our country is to increase the number of cytogenetic laboratories, bearing in mind the results that indicate that molecular and genetic analysis directly determine the prognosis in the treated patient, but also oncological therapy of anaplastic gliomas directly depends on its cytogenetic characteristics. which would exclude a general approach to the treatment of anaplastic gliomas, but we would apply different therapeutic modalities depending on the characteristics of the tumor, i.e., an individual approach to each patient.

CONCLUSION

The incidence of anaplastic gliomas operated on in the Department of Neurooncology of the Clinic for Neurosurgery of the Clinical Center of Serbia corresponds to their frequency, which is published in the available literature.

During the follow-up period, a significantly higher incidence of oligoastrocytomas is observed, which is explained by the impossibility of determining the isocitrate dehydrogenase mutation and 1p / 19q codeletion, which could be used to classify most high-grade gliomas with mixed or ambiguous histology as anaplastic IDH mutant oligodendroglioma with 1p / 19q codeletion.

The application of different chemotherapy modalities does not show statistical significance in the length of survival, in the follow-up period.

Bearing in mind that RT was applied in all patients in whom the Karnofsky score was over 70, we were not able to estimate the prognostic value of RT application.

The radical nature of the operation has statistical significance in the length of patient survival, which confirms the conclusions of most of the conducted studies cited in oncology textbooks.

ACKNOWLEDGEMENTS

None

CONFLICT OF INTERESTS

The authors declare that there was no conflict of interest regarding this manuscript.

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