Surgery of high grade gliomas - pros in favor of maximal cytoreductive surgery

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Abstract

Background: Malignant glioma is the most common primary brain tumour in adults. More and more studies are focused on the role of surgery in prolonged median of survival and survival at two years. The purpose of this study is to add some arguments in favour of radical surgery in malignant glioma.

Material and Methods: The study is based 433 cases of high grade cerebral glioma operated between 01.01.2000-31.12.2009 at the Department of Neurosurgery, Cluj County Emergency Hospital. We analyzed age, gender, type and duration of symptoms, type of surgery, pathological diagnosis and the correlation of these factors with overall survival. Data for long term follow up were available for 266 patients.

Results: The results shows, according to their histological features, the fallowing dispersions: astrocitomas grade III (28%), glioblastoma multiforme (64%), high grade oligodendrogliomas (5%) and high grade ependimomas (3%). The global survival rate was 47 % at 12 months, 26,3% at 18 months and 16,7% at 24 months. The age and type of surgery are prognostic factors that significantly influenced the survival at 12, 18 and 24 months (9,3 months age <65 years versus 7,1 months age >65 years; 9,2 months GTR versus 6,4 months STR-at 12 months monitoring; 11,7 months age <65 versus 7,7 months age >65; 11,5 months GTR versus 7,1 months STR-at 18 months monitoring; 12,8 months age <65 versus 8 months age >65; 12,6 months GTR versus 7,5 months STR –at 24 months monitoring).

Conclusions: Our study shows that long term postoperative outcome after radical surgical resection are better than the results of either partial resection or simple biopsy; in terms of duration of survival (the difference of mean survival at 12, 18 and 24 months monitoring was 2,8 months, 4,4 months and 5,1 months respectively in favour of patients with gross total removal) .

Keywords: anaplastic astrocitoma, anaplastic ependymoma, glioblastoma multiforme, gross total removal (GTR), high grade glioma, malignant oligodendroglioma, subtotal removal (STR).

Introduction

High grade gliomas are aggressive cancers. The World Health Organization grading system recognizes grade III and grade IV primary brain tumors of astrocytic,

oligodendroglial or mixed lineage. Despite advances in surgical techniques, and improvement in radiation treatment and chemotherapy, the median survival of these patients has changed little over the last decades.

Identification of these tumours is usually easy by symptoms such as headaches, seizures or focal weakness or numbness, with imaging findings of an enhancing mass lesion. There are two major aspects of gliomas biology that contributes to its poor prognosis: the formation of new blood vessels through the process of angiogenesis and the invasion of glioma cells. The most severe form, glioblastoma multiforme, has a marked and diffuse infiltration through the normal brain parenchyma. Health-related quality of life of these patients has always been poor. Patients with a presumed primary brain tumour from clinical examination and radiological investigation have two initial surgical management options: biopsy or resection [25,26].

The goals of surgery for malignant glioma, as postulated by Shapiro [28], are as follow:

(1) The establishment of a histological diagnosis.

(2) Tumor cytoreduction for:

(a) Improvement in neurological status by reduction of increased intracranial pressure,

and (b) Possible change in tumor kinetics.

In the recent EORTC trial [32] surgery seems to have no prognostic role concerning the survival rate. Latest studies are focused on the role of surgery in prolonged median of survival and survival at two years. The purpose of this study is to add some arguments in favour of surgery and especially of the radical surgery in malignant gliomas.

Patients and methods

This is a retrospective study of a single centre, single surgeon and represents the last ten years of the senior author. The study is based on 433 cases of high grade cerebral gliomas operated between 01.01.2000 and 31.12.2009. at the Neurosurgical Department of Cluj County Emergency Hospital. Patients considered for the study were adults and children aged from 6 to 82 years old with the initial diagnosis of a malignant glioma. All the tumours were operated and gross total removal was the goal in all of the cases. The extent of surgery was reported by the neurosurgeon as partial or total removal, and confirmed on enhanced CT or MRI in the first 24-48 postoperative hours. The tumours were histological proven high grade gliomas. Data for long term follow up were available for 266 patients.

The following statistic methods have been used for group description:

- Descriptive: the distribution value (mean ± standard deviation, confidence interval, min/max values, contingency tables and frequencies.

- Analytical: the survival analysis and the disease free interval depending on age, pathological diagnostic, surgical procedure/resection type through Kaplan-Meier method and the evaluation of a difference of survival existence between groups through log-rank test.

The group of 266 patients have been split for the analysis of survival from surgery to 12, 18 and 24 months as it follows:

- for observing the disease free interval at 12 months all the 266 patients were included in the group

- for observing the disease free interval at 18 and 24 months 228 patients were included (patients operated in 2009 have been excluded).

All analyses were done with SPSS.

Results

Between the 1st t of January 2000 and the 31st of December 2009, 433 malignant glioma have been operated. From all the cerebral tumour cases operated in this period (1861 cases) malignant gliomas represent 23.26%. In this period the temporal distribution of cases varied, the peaks being present in 2005 (79 cases out of 238 operated tumours) (Figure 1)

The patients were aged between 6 and 82 years old. Most of the malignant glioma cases have been recorded in the fifth decade.

From pathological point of view the glioblastoma multiforme was met in most of the cases (64%), followed by anaplastic astrocytoma (28%). The malignant oligodendroglioma and anaplastic ependymoma were met in 5%, 3% respectively.

The most frequent symptom of the patients while they were admitted in our hospital was the increased intracranial pressure (ICP) (78%) followed by focal weakness, seizures (18.9%), and aphasia (11.5%). The interval between the debut of symptoms and admission in the hospital was one month for 39% of cases. An evolution of symptoms longer than 6 months has been met for 12% cases (Figure 3).

The anaplastic astrocytoma have been diagnosed in 123 cases (28% of all the malignant glioma). Having males as majority (62%) and the peak incidence between 40-49, the total removal has been reached in 83, 10% of the cases.

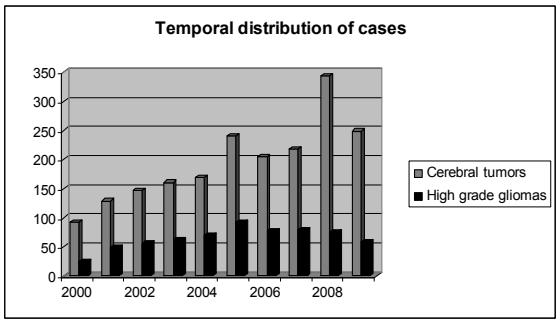


Figure 1 Distributions of cases in the studied interval

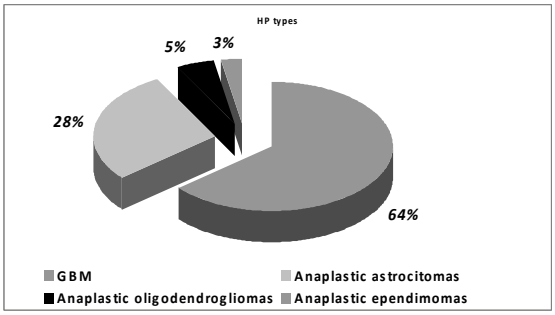


Figure 2 Pathological distribution of malignant gliomas in the present study

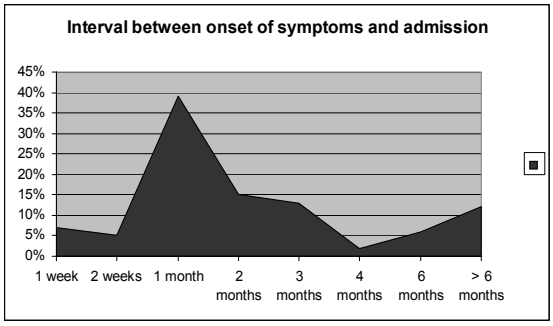
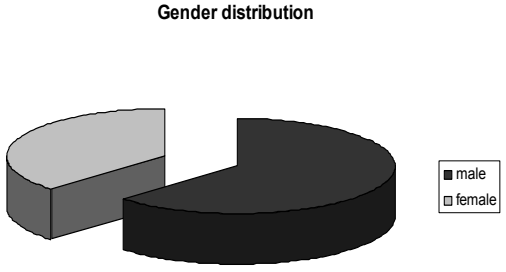


Figure 3 Interval between onset of symptoms and admission



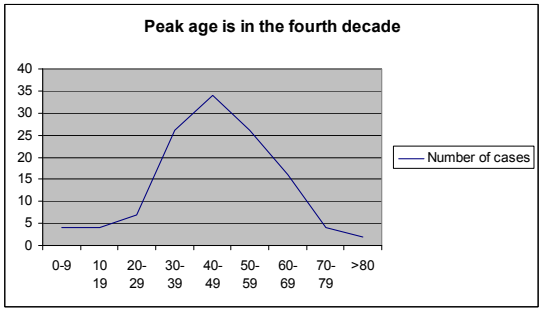


Figure 4 Gender and age distribution of Anaplastic Astrocitoma cases

The lobar localization of the tumour was met in 61.4% (Figure 5.) of the cases, and in 30.1% of the cases it was multilobar. The posterior fossa localisations and the intraverticular one were met at 6%, and 2.5% respectively.

The glioblastoma multiforme was met in 276 cases (64% from all the malignant tumours). The sex distribution has shown a majority of males (55.5%). Unlike the anaplastic astrocitoma the most affected ages were between 50-59 (100 cases)(Figure 6).

The gross total removal has been obtained in 87,5% cases. The lobar localization has been considered as majority in this case (58,6%), the glioblastoma multiforme with multilobar localization being met in 36,8% of the cases. There were descriptions of the localizations at the callosal (1,8%) (Figure 7), posterior fossa (1,4%) and ventricles (1,4%).

The malignant oligodendrogliomas and anaplastic ependymomas were met in 5%, 3% respectively. In both situations there have been a male majority and the most affected was the fifth decade of life. The total removal was reached in most of cases.

The global survival rate for 266 patients included in our study was 47 % at 12 months, 26,3% at 18 months and 16,7% at 24 months. (Table 1)

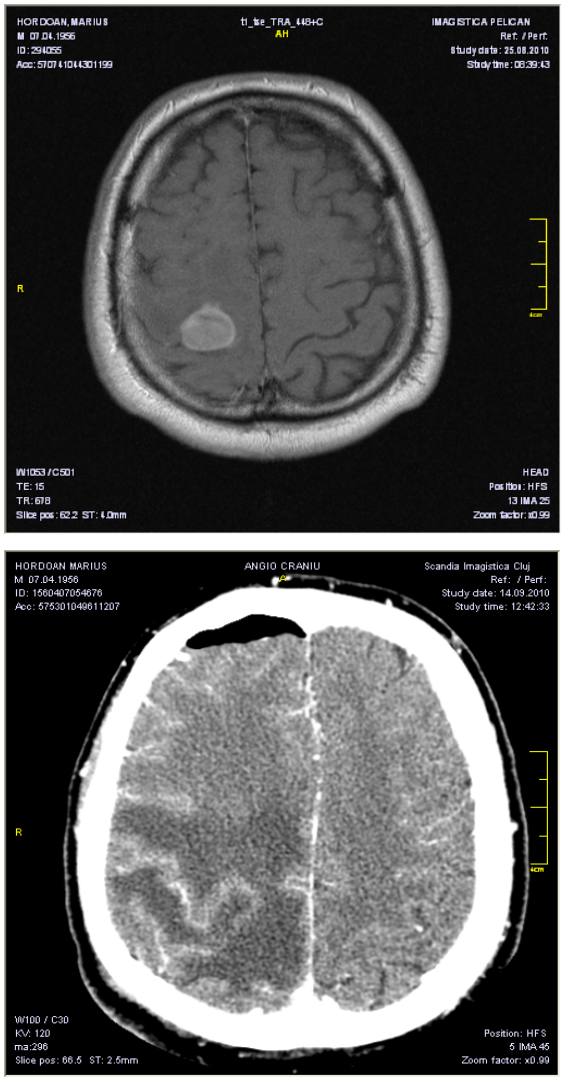


Figure 5 Preoperative enhanced MRI and postoperative contrasted CT scan of a lobar anaplastic astrocytoma

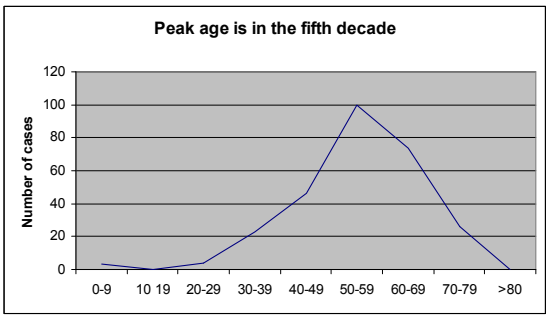


Figure 6 Age distribution of Glioblastoma cases

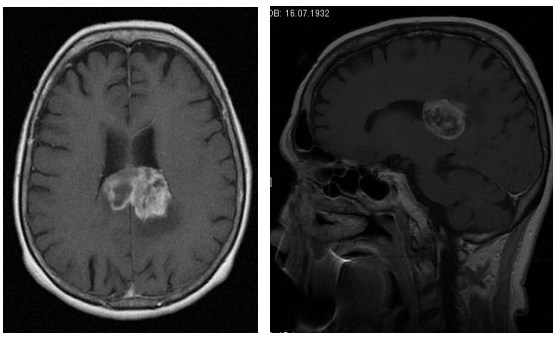
TABLE 1
Overall survival at 12, 18 and 24 months

Disease free interval	Number of patients	Global survival rate	Survival mean rate (months)	Survival median rate (months)
12 months	266	47%	8,87 months **CI**-95%: 8,41-9,43	11
18 months	228	26,3%	10,96 months **CI**-95%: 10,20-11,72	11 **CI**-95%: 9,91-12,08
24 months	228	16,7%	11,96 months **CI**-95%: 11,01-12,91	11

TABLE 2
Disease free interval regarding the age, type of surgery and pathological findings

Disease free interval	Log Rank (Mantel-Cox) factor: age (<65 years/ ≥65 years)	Log Rank (Mantel-Cox) factor: type of surgery (gross total removal/subtotal removal)	Log Rank (Mantel-Cox) factor: histopatholgical diagnosis	Log Rank (Mantel-Cox) factor: gender
12 months	**0,000**	**0,000**	0,090	0,296
18 months	**0,000**	**0,000**	0,122	0,836
24 months	**0,000**	**0,000**	**0,031**	0,756

The age and type of surgery are prognostic factors that significantly influenced the survival at 12, 18 and 24 months, meanwhile the pathological diagnostic significantly influenced the survival only at 24 months (Table 2)



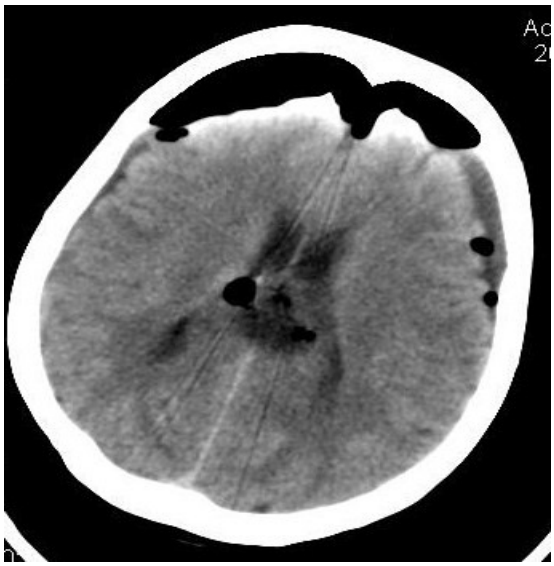


Figure 7 Preoperative enhanced MRI and postoperative CT scan of a completely removed Glioblastoma Multiforme of corpus callosum

From all 266 cases, the gross total removal (GTR) was reached in 229 patients, while the subtotal removal (STR) of tumours was performed in 37 cases.

There has been a significant difference between expected frequencies and the observed ones in resection type that concerns survival. At 12 months monitoring, the survival was around 9,2 months in patients with GTR, with a confidence interval between 8,7 and 9,7, meanwhile in the STR group the survival mean was 6,4 months, with a confidence interval of 95% from 5,2 to 7,7. (Table 3, Figure 8)

TABLE 3

Mean survival time at 12 months monitoring in patients with GTR and STR respectively

Type of surgery	Mean(a)			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Gross total removal	9,263	,244	8,784	9,741
Subtotal removal	6,478	,640	5,223	7,734
Overall	8,875	,236	8,413	9,337

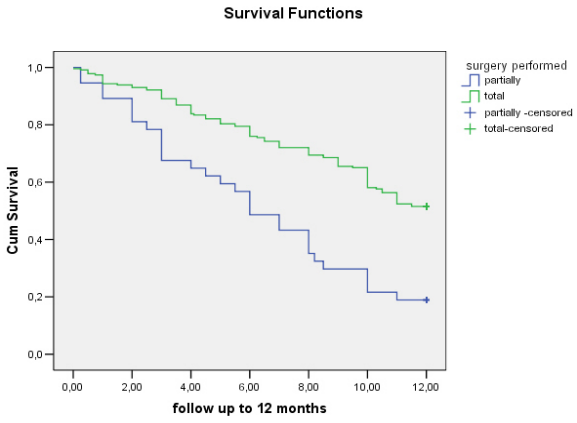


Figure 8 Type of resection as a prognostic factor at 12 months monitoring

Similar findings are found at 18 months interval monitoring , the survival mean for patients with GTR has been of 11.5 months (with a confidence interval of 95% from 10,7 to 12,4), significantly higher than survival rate for STR group (7,1 months, with confidence from 5,5 to 8,7, $p<0,005$) (Table 4, Figure 9).

The survival monitoring at 24 months also highlighted a significant difference of survival between GTR and STR groups ($p< 0,005$). The survival mean at GTR group was of 12,6 months, compared to the 7,5 months one for the STR group (Table 8, Figure 4).

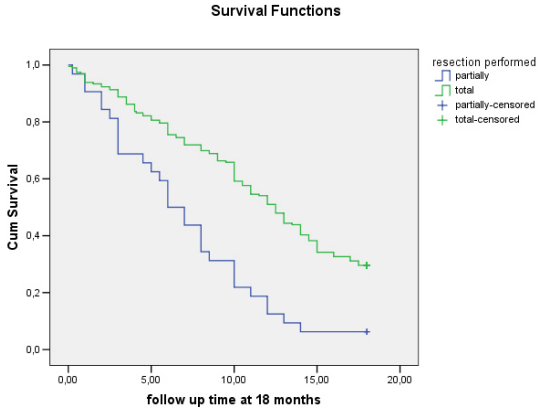


Figure 9 Mean and median survival time and survival graphic at 18 months depending on the type of surgery

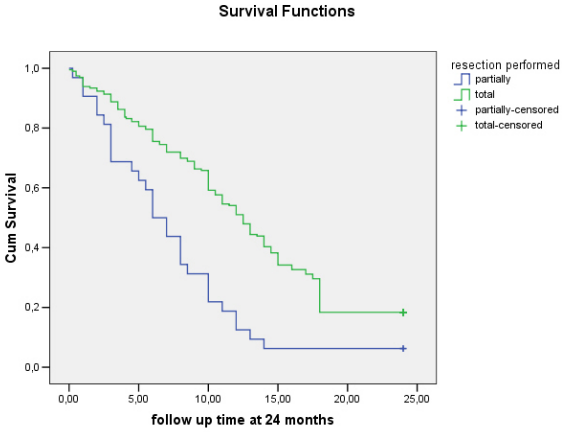


Figure 10 Mean and median survival time at 24 months depending on the type of surgery

TABLE 4

Mean survival time for 18 months monitoring

Type of surgery	Mean(a)				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Gross total removal	11,592	,414	10,780	12,405	12,500	,673	11,182	13,818
Subtotal removal	7,133	,822	5,522	8,744	6,000	,849	4,337	7,663
Overall	10,966	,388	10,205	11,727	11,000	,552	9,917	12,083

TABLE 5

Mean survival time at 24 months monitoring

Type of surgery	Mean(a)				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Gross total removal	12,694	,521	11,673	13,715	12,500	,673	11,182	13,818
Subtotal removal	7,508	,998	5,551	9,464	6,000	,849	4,337	7,663
Overall	11,966	,484	11,018	12,915	11,000	,552	9,917	12,083

For determining the role of age as a prognostic factor all the 266 patients were split in 2 groups: one under 65 years old and another one above 65. The first group contained 213 patients and the second one 53 patients. The survival rate had been observed at 12, 18 and 24 months. In all situations a statistic association has been found between age and survival. The younger patients had a better survival than the ones over the age of 65 (Table 6,7 and 8). Meanwhile in the under 65 years of age

group the mean survival was of 9,3 months (with lower bound at 8,802 and the upper bound at 9,797), in the group over 65 the mean survival was of 7,1 months with the lower bound at 6,113 and the upper bound at 8,228. The difference was more significant at the 18 months monitoring, with a difference of mean survival of 4 months in favour of the younger group. At the 24 months monitoring the difference was also significant, with a mean of 4,8 months in favour of the patient younger than 65.

TABLES 6, 7 AND 8

Mean and median for survival time at 12,18 and 24 months

Age	Mean(a)				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
<65 years	9,300	,254	8,802	9,797	.	.	.	.
=>65 years	7,171	,539	6,113	8,228	8,000	1,211	5,626	10,374
Overall	8,875	,236	8,413	9,337	11,000	.	.	.

Age	Mean(a)				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
<65 years	11,714	,420	10,891	12,537	12,500	,715	11,098	13,902
=>65 years	7,750	,825	6,133	9,367	6,500	1,366	3,823	9,177
Overall	10,966	,388	10,205	11,727	11,000	,552	9,917	12,083

Age	Mean(a)				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
<65 years	12,882	,535	11,833	13,930	12,500	,715	11,098	13,902
=>65 years	8,029	,922	6,221	9,837	6,500	1,366	3,823	9,177
Overall	11,966	,484	11,018	12,915	11,000	,552	9,917	12,083

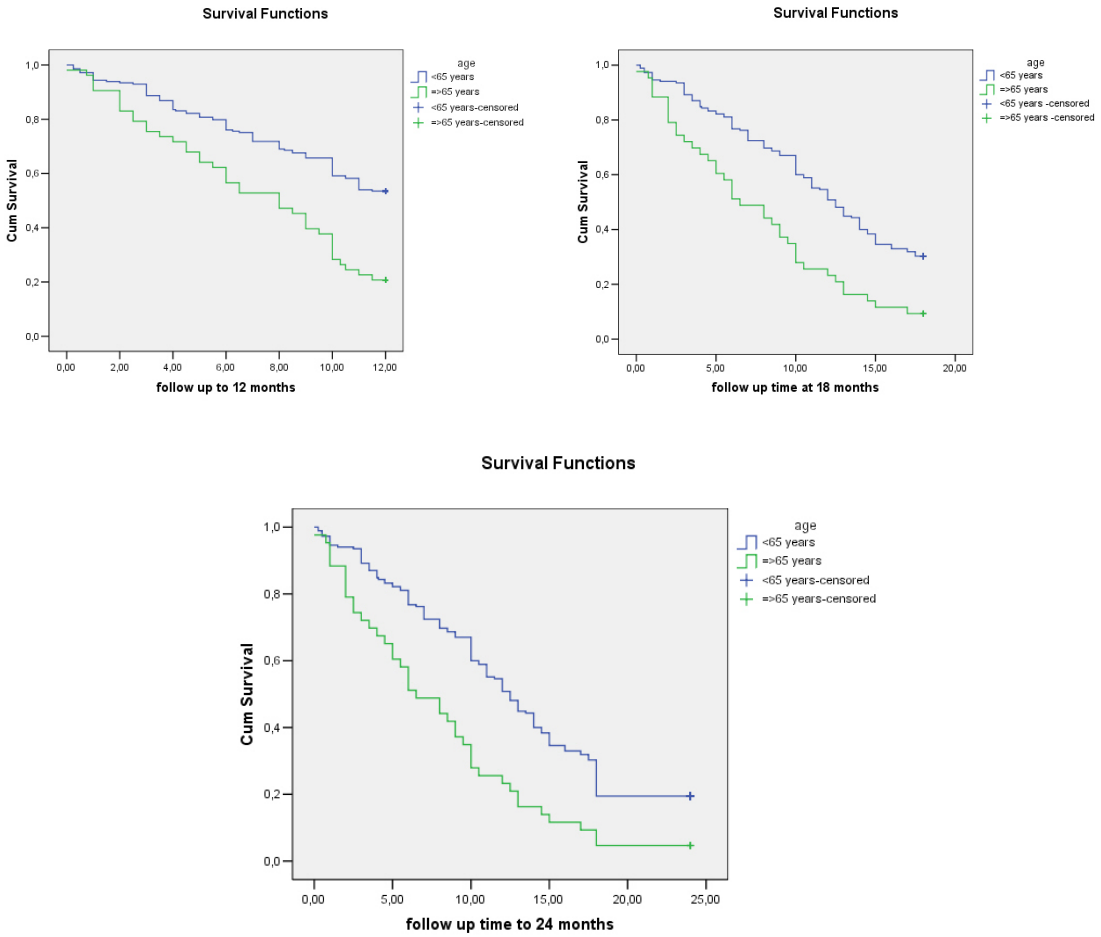
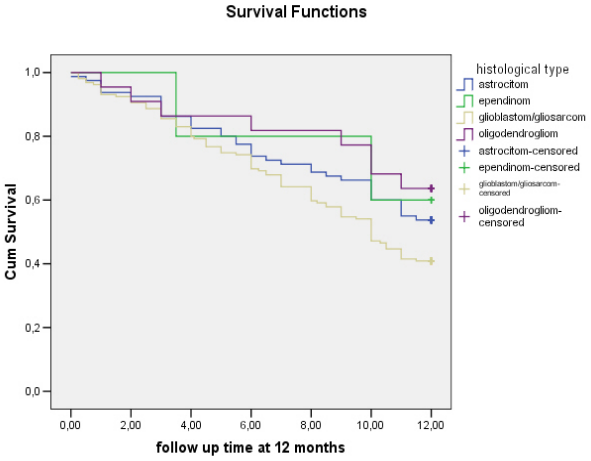


Figure 11 Survival graphic at 12, 18 and 24 months depending on age

Regarding de pathological findings, there is no statistical significant difference at 12 and 18 months monitoring (p=0.09 respectively p=0,122). For survival at 24 months, the survival mean for glioblastoma multiforme diagnosed patients was of 11,2 months, for the ones having anaplastic astrocytoma was of 11,9 months. Patients with malignant oligodendrogliomas survived approximately for 16,1 months (with a confidence interval of 95% between 12,6 and 19,6) and the ones with malignant ependymoma for 17,1 months (p=0.031). (Table 9)



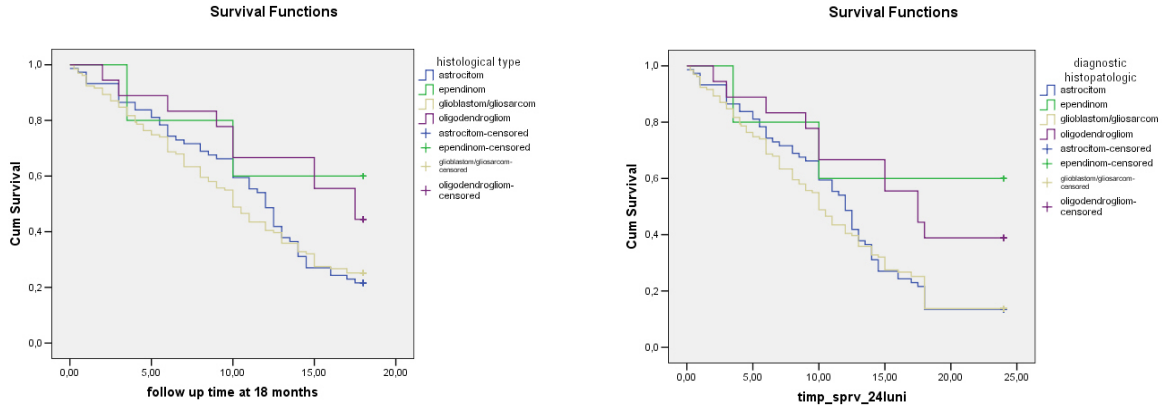


Figure 12 Survival functions depending on the pathological findings at 12, 18 and 24 hours monitoring

TABLE 9

Mean and median survival time depending on pathological findings at 24 months monitoring

Pathological diagnostic	Mean(a)				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Anaplastic astocytoma	11,946	,786	10,406	13,486	12,000	,645	10,736	13,264
Anaplastic ependymoma	17,100	3,889	9,477	24,723	.	.	.	.
Glioblastoma multiforme	11,205	,632	9,966	12,444	10,000	,715	8,598	11,402
Anaplastic oligodendrogliomas	16,167	1,795	12,648	19,685	17,500	2,635	12,335	22,665
Overall	11,966	,484	11,018	12,915	11,000	,552	9,917	12,083

Discussions

The treatment of patients with high-grade gliomas remains a challenge for modern therapy. Clear treatment guidelines regarding the extent of surgery, derived from randomized prospective studies in the literature do not exist, and there are some controversy regarding the best treatment for malignant brain tumours. The gold standard for high-grade gliomas includes combination of surgery, radiotherapy, and chemotherapy.

High grade gliomas are widely infiltrative , fact them makes quite impossible to completely resect, even in cases of hemispherectomy, procedure that

was pioneered by Walter Dandy in 1928[6]. In order to achieve the cure of this highly malignant tumours some other authors have been presented their results with hemispherectomy, although associated with a poor postoperative survival rate, but also with a recurrence of tumours in an interval of less than two years [3,6,12,23]. Despite of impressive progress of the last two decades in terms of neuroimagistic diagnostic, despite of the new inraoperative tools namely neuronavigation, ultrasonography, awake neurosurgery or introperative MRI, the nowadays neurosurgical results in malignant gliomas are still disappointing in terms of long term survival [17].

Usually tumour recurrence occurs close to the resection margin, were the cell density is increased. Outside of this region the cell density drops sharply as the distance from the resection cavity increases, an argument in favour of a wider resection margin which presumably could delay recurrence[1, 3].

In a review of literature Ryken et al. [24] selected thirty qualitative papers, 10 prospective studies and twenty retrospective studies. Five of the prospective studies provided Class II data [2, 15, 30, 31, 35] and one of the 20 retrospective studies provided Class II data [15]. All, but one of these better quality studies support extent of resection as a factor in improving survival in newly diagnosed adult patients with malignant glioma. Of these only the study of Levin published in 1985[17] failed to support extent of resection for glioblastoma, but did demonstrate a survival advantage in cases of anaplastic astrocytoma. Of the remaining retrospective papers reviewed, all provided Class III data. Fourteen studies of the nineteen provided data, which supported the concept of cytoreductive surgery in the initial management of malignant glioma. Some of these reviewed studies are presented in summary.

In 2003, Metcalfe and Grant provided an update on the Cochrane report of 2000 on biopsy versus resection for malignant glioma [19]. After a search of over 2,100 documents, the authors failed to locate enough randomized data for analysis; therefore no conclusion could be drawn. A recommendation was made calling for randomized prospective study of this important issue.

Stummer et al.[31] describe a prospective study evaluating the extent of resection and its influence on survival employing 5-aminolevulinic acid, a fluorescent marker . Focused on the novelty to the radical resection of gliomas using a fluorescent marker to aid in desection decision, the study underlines in subsidiary the advantage of gross total removal over de subtotal resection in terms of survival in multivariate analysis.

In the same review of Ryken [24], Bricolo et al. are mentioned with a preliminary report of a prospective data collection on patients with presumed malignant glioma subjected to an aggressive surgical strategy and assessed postoperatively with CT scanning placing them either in a gross total resection or subtotal resection (10–15% remaining enhancement) group. While no statistical analysis is provided the authors report at 60% 1 year survival for their gross total resection group versus only 24% in the subtotal resection group.

Lacroix et al. [17] found that surgical resection of 98% or more of the contrast-enhancing tumour volume is an

independent variable associated with longer survival times in patients with glioblastoma multiforme. As a consequence their recommendation is that gross-total resection should be performed whenever possible for these patients, yet not at the expense of neurologic function or surgical complications.

In the study of Nitta et al. of 101 patients with malignant glioma including 68 patients with GBM and 32 with anaplastic astrocytoma who underwent operative procedures followed by a uniform radiotherapy and chemotherapy regimen [22], the authors found that in the glioblastoma group the patients undergoing gross total resection as judged by postoperative CT survived significantly longer than patients undergoing either a partial resection (less than 75%) or subtotal resection (75—less than 100%). They suggested that gross total excision might aid in the adjuvant therapy following surgical intervention.

Devaux et al.[7] in a retrospective study of 218 patients with newly diagnosed malignant glioma including 164 patients with Grade IV tumours and 54 patients with Grade III tumours found that using a detailed surgical approach designed to achieve volumetric resection was of benefit in prolonging survival in Grade IV patients even after adjustment for no clinical prognostic factors.

As a result, it follows that the majority of the reviewed data supports maximal cytoreductive surgery.

In our retrospective study of 266 cases that met inclusion criteria for statistical monitoring at 12, 18 and 24 months, the obtained data also supported maximal cytoreductive surgery in order to prolong survival of patients with malignant gliomas. In this study only GTR with STR are compared, based on the senior author intraoperative impression and confirmed on immediate postoperative enhanced CT scan or MRI. Based on postoperative imaging we consider STR any contrasted remnants visible on more than two adjacent slices from the initial volume of tumour. At 12 months monitoring, the survival was around 9,2 months in patients with GTR, with a confidence interval between 8,7 and 9,7, meanwhile in the STR group the survival mean was of 6,4 months, with a confidence interval of 95% from 5,2 to 7,7. Similar findings are found at 18 months interval monitoring, the survival mean for patients with GTR was of 11.5 months (with a confidence interval of 95% from 10,7 to 12,4), significantly higher than survival rate for STR group (7,1 months, with confidence from 5,5 to 8,7, $p<0,005$). The survival monitoring at 24 months has also highlighted a significant difference of survival between GTR and STR groups ($p< 0,005$). The survival mean at GTR group was of 12,6 months, comparing to 7,5 months for the STR group. As it is shown, the difference increases from almost three months on the first period of monitoring (12 months) up to 5 months in the 24 months monitoring period. A median survival difference from three months up to five months between GTR and STR represents findings that are consistently in favour of maximal cytoreduction, at least in our opinion. Based on our data we consider our study a class III recommendation.

Failure to demonstrate prolonged survival with Class I data should not stop physicians from considering surgical resection thanks to the numerous other benefits of tumour removal.

The obvious benefits from glioma

resection are symptomatic relief from mass effect and obstructed cerebrospinal fluid. The tumoral mass produces compression of neural pathways and distortion of brain structure that contribute to both general symptoms and focal deficits and explain the neurological improvement following surgical resection. After surgery there are some global symptoms (headache, nausea, vomiting, general malaise) that show dramatic improvement (11). The partial reversal of neurological deficit is due to the relief of local compression (36). Dexamethasone in dose of 16 mg per day has been proved an useful indicator of potential neurological improvement after glioma resection. Patients who show improved functional status after steroid administration will be the one with improvement in quality of life after aggressive surgical resection, provided that there is low postoperative morbidity (20).

A number of authors observed that partial tumour resection is associated with greater risk of postoperative neurological worsening than either radical excision or stereotaxic biopsy [5,14,25,29]. In the series of Ciric et al [5] 97% of patients with gross total or nearly gross total resection had improved or stable postoperative neurological status; in contrast, postoperative neurological worsening occurred in 40% of patients with partial resection. In two other series Fadul et al [8], Vecht et al, [34] no significant difference was found in the incidence of neurological worsening following gross total resection compared to limited resection. These data from various studies suggest that radical tumour resection is associated with no greater or perhaps less risk of neurological compromise than with partial resection.

In our experience we also could document a global improvement of neurological status in more than 85% of the GTR operated cases, with a less than 10% rate of neurological complications, and a mortality rate below 4%, large majority of them being patients with more than 70 years of age.

Related to age there are some studies that provide useful data regarding elderly patients, namely those over 65 [4,35]. In the latest study of Chaichana (2010)[4] they found that patients who underwent surgical resection had median survival of 5.7 months, while patients who underwent needle biopsy without resection had median survival of 4.0 months. Although modest in absolute terms, older patients did have significantly prolonged survival with aggressive resection as compared to needle biopsy, without an increase in surgical morbidity or mortality. Their study demonstrates that older patients undergoing aggressive resection did not have an increase in surgical morbidity, and had prolonged survival as compared to matched older patients undergoing needle biopsy. Older patients, as with younger patients, may therefore benefit from aggressive surgical resection, and aggressive resection should be considered for older patients who present with GBM.

We are also in favour of aggressive surgery in patients older than 65, despite the fact that their median of survival is significantly lower than that of the younger patients. Meanwhile in the under 65 years old group the mean survival was 9,3 months (with lower bound at 8,802 and the upper bound at 9,797), in the group over 65 the mean survival was 7,1 months with the lower bound at 6,113 and the upper bound at 8,228. The difference was more

significant at the 18 months monitoring, with a difference of mean survival of 4 months in favour of the younger group (11,7 vs. 7,7 months), difference which is also maintained at the 24 months monitoring (12,8 versus 8,0 month). Despite the fact that we compare only patients with GTR and STR, without Needle biopsy sampling, and considering the recent provided data from the Chaichana's study, we can conclude that maximal cytoreduction surgery is recommendable in the elderly patients, mentioning also the fact that the mortality is higher in the group of patient over 65.

The mechanical cytoreduction of the mass also obtains time for other therapeutic interventions (radiotherapy, chemotherapy, and immunotherapy). The reduced tumour burden has been shown to have a beneficial effect on cerebral blood flow and metabolism even at sites in the brain distant from tumour resection.

One hundred grams of tumour mass is considered lethal for the average adult. Along with surrounding edema, the tumoral mass accounts for 10% of the intracranial volume. For the neurologic symptoms to appear it generally takes 30 to 60 g of tumour or 3 to 6x1010 cell. 1 g of tumoral mass or 1x109 cell is thought to be left after a total resection of the gadolinium enhancing regions on magnetic resonance imaging. The adjuvant therapy of malignant glioma also contributes to tumoral reduction. While radiotherapy kills two logs of cell, chemotherapeutic regimens are thought to kill one to two logs of cell. The body's immune mechanisms are believed to suppress tumour burdens less than 1x105 cells. Despite these promising assertion , malignant glioma remains for the vast majority of patients an incurable disease (16).

The efficacy of adjuvant therapy is increased when the tumour load is lower. A higher glioblastoma load increased chemotherapy resistance as it was demonstrated in an in vivo study. In order to achieve the same effect, a 4-fold increase in the glioblastoma load requires a 2-fold increase in the BCNU concentration (21).

Other argument in favour of open surgery is the accuracy of histological diagnosis, which is dependent on the size of the tissue sample. As a result of limited tissue samples, the stereotactic biopsy is associated with false negatives, with is estimated to be around 10% (27). A discrepancy rate of 38% between biopsy and subsequently resected specimens in 81 patients was reported by Jackson et al (13). In 26% of cases, this discrepancy was found to affect the treatment. For the 38% of cases the prognosis was altered.

Concerning the pathological findings, not surprisingly in our study there is no statistical significant difference at 12 and 18 months monitoring ($p=0.09$ respectively $p=0,122$). For survival at 24 months, the survival mean for glioblastoma multiforme diagnosed patients was 11,2 months, for the ones having anaplastic astrocytoma was 11,9 months. Patients with malignant oligodendrogliomas survived for approximately 16,1 months (with a confidence interval of 95% between 12,6 and 19,6) and the ones with malignant ependymoma 17,1 ($p=0.031$).

Finally surgical resection of large sample of tumour may serve as an aid in research. The collection of large human tumour samples allows for comprehensive molecular analysis and fingerprinting of each tumour [9,33] , which in turn may lead to the development of individually-

tailored molecular therapies. Increasing evidence suggests that tumors of the central nervous system are derived from proliferatively active neural stem cells residing in defined neuropoietic niches of the adult brain. These cancer stem cells, also identified in other tumors, provide a reservoir of cells with self-renewal capabilities, can maintain the tumor by generating differentiated non-stem tumor cells and are responsible for recurrences after ablative neurosurgical therapy and chemoradiotherapy.

The only way to successfully control recurrent malignant gliomas and even hope for a cure in the future is by combining standard chemotherapy with immunotherapy. Despite the apparent improvements of current treatments, it should be realized that the characteristic brain tumor niche may provide recurrent gliomas an "escape mechanism" from anticancer treatments. Thus, the use of targeted molecular therapy drugs may effectively inhibit or at least slow down cancer stem cell proliferation and stop the brain microenvironment from allowing furtive invasion and proliferation of highly aggressive malignant gliomas[9]. Only through further understanding of the biology of gliomas can we hope to find a cure in the future.

Conclusion

The review of the literature suggests that gross total resections for patients with malignant gliomas can improve both survival and quality of life. Different studies show that early and long term postoperative outcome after radical surgical resection are better than the results of either partial resection or simple biopsy, in terms of neurological status and duration of survival. Similarly, reoperation for recurrence of glioma offers reasonable extension of quality survival.

Our study provides a new argument in favour of gross total removal. We have shown that radical surgery improves the overall survival and total resection should be considered whenever possible. An aggressive cytoreduction is recommendable also in patients over the age of 65. Total removal for patient with tumour recurrence does not change statistically significant the global survival comparing to partial removal but the quality of life sure benefits from it, by decreasing the intracranial pressure.

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