



THE LENGTH OF SURVIVAL IN PATIENTS WITH HIGH GRADE ASTROCYTOMAS

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Summary: A retrospective analysis of the length of survival in operatively treated patients harboring a Grade III and Grade IV astrocytomas in a 5-year period (1985–1989) was carried out in our investigation. There were 121 patients with the above mentioned tumors, sixteen of them were excluded from further analysis because of a lack of adequate follow-up, an age of less than 18 years, and deaths in the early postoperative period mostly due to cardio-pulmonar complications. Of the 105 remaining patients, 69 had Grade III tumors (65.7%) and 36 Grade IV tumors. The male-female ratio was 71:34 (67.6:32.3%). The majority of them were older than 40 years (91.42%), only 9 patients were less than or equal to 40 years of age. The one year survival rate had 1/3 of patients, two-years survival was found in 7% of patients, there were 5% long-term survivors (more than 3 year-survival rate) and only 1 patient lived longer than 5 years. Longer survival was found in patients younger than or equal to 40 years of age ($p < 0.001$), in patients with Grade III tumors ($p < 0.024$), in patients who were treated by chemotherapy ($p < 0.017$) and in those who underwent a repeated surgery ($p < 0.00001$). The sex had no statistical significance in relation to the survival rate. All patients were treated with 42 Gy, 14 of them received chemotherapy ($p < 0.017$) as well. In the group of 15 patients who had repeated surgery, proportionally more frequent were males 12 (16.9%), as well as patients who were younger than or equal to 40 years of age ($p < 0.087$). The length of survival after a repeated surgery was 3–4 times shorter than after the first operation. The multidisciplinary treatment of high-grade astrocytomas may contribute to long term survival but real perspectives in the duration of life in these patients might be expected after active immunologic treatment.

Key words: Astrocytoma, chemotherapy, repeated surgery, survival

Introduction

The length of life and its quality are the basic parameters through which one can determine the outcome of any operation. Observing this aspect high grade astrocytomas (III and IV) represent strikingly important neurosurgical and oncological problem and together with some leucosis and lymphoid tumors they are tumors with gloomy prognosis (1).

As early as 1932 Cushing (2) reported a very low survival rate in high grade astrocytomas after operation in a series of 183 tumors with only one 44-year old patient who lived longer than 42 months. Frankel and German (3) in their series of 219 patients operated on due to malignant astrocytomas reported two-year survival rate in 11%, three-year survival rate (the long term survival) in only 3% and one patient lived 5 years after operation.

Nevertheless the introduction of radiation and chemotherapy, especially in the first postoperative year, has given better effects concerning the duration of life and survival rate. Walker et al (4) reported approximately the same survival rate.

New diagnostic methods as well as the microsurgical technique in several studies (5,6) after 1980 did not significantly improve the survival rate, and 5-year survival is still sporadic.

Salcman et al (1) prospective study comprising 289 patients with malignant astrocytomas operatively treated in a 10-year period (1978–1988) is one of rare studies with a significantly higher percent of long term survival rate (a 3-years survival going up to 20%, and even 6% for those who lived more then 5 years).

The objective of this study is to analyze the survival rate of patients with high grade astrocytomas operatively treated, to discuss factors which influence the survival and to correlate data

with the available literature.

Patients and Methods

In patients with a Grade III tumors and Grade IV tumors which were operated on in five year period (1985–1989) the survival rate was evaluated. The analysis comprised 121 patients (older than 18 years of age) with supratentorial high grade astrocytomas. Sixteen of them were excluded from further analysis because of inadequate follow up, and short postoperative fatal outcome due mostly to cardio–pulmonar complications.

All patients were treated postoperatively by radiation (42 Gy), according to oncological protocol, while a small number of patients was also treated by chemotherapy. Patients in whom chemotherapy was interrupted after the first or second course of treatment due to impairment of the general condition or abnormal laboratory findings were not included in the group of patients who were treated by chemotherapy. The repeated operation was performed only in patients where the oncological treatment was completed.

The data were statistically performed and analyzed using Chi–square test and the Kaplan–Meier survival curve.

Results

In a series of 105 patients (Table 1) 69 had a Grade III tumors (65.7%) and 36 had Grade IV tumors. There were 71 male (67.6%) and 43 women with the ratio of 2.1:1. The same ratio was in both subgroups of astrocytomas. Older patients dominated in both subgroups, with 96 patients (91.4%) older than 40 years of age.

The survival curves of all 105 patients are shown on Fig. 1 along with the Kaplan–Meier survival curve based on the study by Salcman et al (18). In the first 12 months 2/3 of operated cases died, only 7% were alive at 2 years, 5% were alive at 3 years, and only 1 patients lived longer than 5 years. The median survival time (the time of 50% of survival rate) was 8 months in contrast to 15 months of the Salcman et al (18) scale. The median survival time was 8 months for patients older than 40 years of age and 14 months for those who were less than or equal to 40 years of age, with out statistically significant difference.

The survival curve depends on age and is presented on the Fig. 2. The Fig. 3 represents the influence of histological grade on the duration of the survival. The median survival time in patients with Grade III was 11 months, and only 6 months

Table 1. Median survival by age, sex and grade (N=105)

Age (years)	Male			Female			Total
	gr. III	gr. IV	Total	gr. III	gr. IV	Total	
18–20	0	0	0	1	0	1	1
21–30	1	1	2	0	0	0	2
31–40	1	2	3	1	2	3	6
41–50	14	4	18	2	2	4	22
51–60	15	7	22	12	5	17	39
61–70	12	10	22	6	2	8	30
>70	3	1	4	1	0	1	5
Total	46	25	71	23	11	34	105

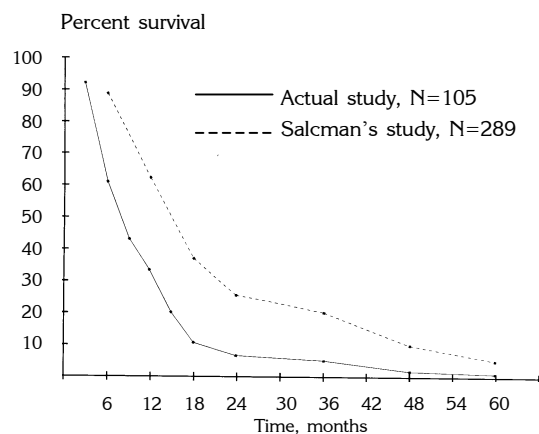


Fig. 1. Survival curve (Kaplan–Meier) for 105 operated patients with malignant astrocytoma compared with Calcman's survival curve

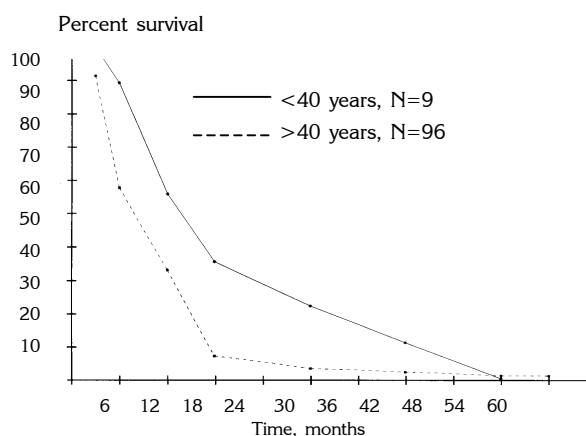


Fig. 2. Influence of age on patients survival

was in patients with a Grade IV tumors.

Fig. 5 showed a statistical significance of

Table 2. Characteristics of patients with repeated surgery

Characteristics	N	Percentage	χ^2	P
Male	71	16.9	1.23	NS
Female	34	8.8		
≤ 40 god	9	33.3	2.92	NS
> 40 god	96	12.4		
Gr. III	69	17.4	15.9	< 0.021
Gr. IV	36	8.3		

The differences in the postoperative treatment can be of striking importance for the duration of survival. Fig. 4 represents a statistically significant difference in the duration of survival in patients treated by radiation and chemotherapy. The median survival time was 17 months, the long term survival was found in 17%, and only 1 patient lived longer than 5 years in contrast to those patients who, postoperatively were treated only by months, two-year survival rate was below 5%, and

repeated surgery relation to the survival rate ($\chi^2=20$. $p<0.00008$). The median survival rate in patients who underwent repeated surgery was 17 months. The survival rate after the repeated surgery was 3–4 times shorter than after the first operation and was 4 months. In this group of patients men were two times as frequent than women. The same relation held for the age (patients ≤ 40 years) as well as for the type of tumor (Grade III tumors).

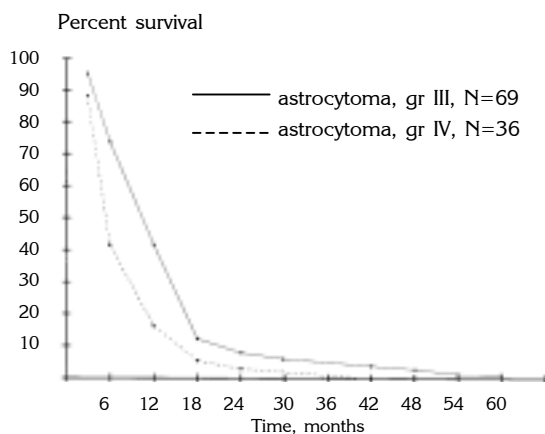


Fig. 3. Influence of astrocytoma histological grade on patients survival

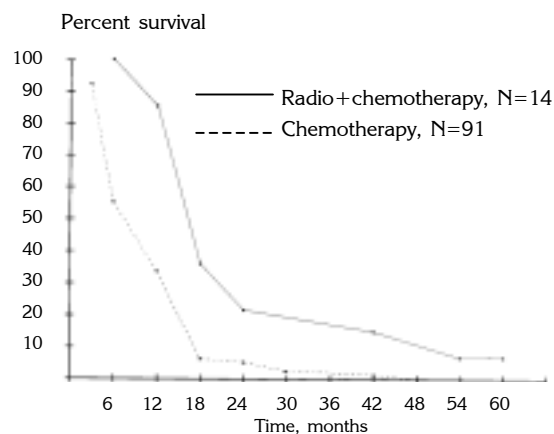


Fig. 4. Influence of mode of treatment on patients survival

there were no 5-year survivors.

Fifteen patients (14,3%) had repeated surgery after CT examination and the clinical course, and only one patient underwent a twice repeated surgery.

Although the median survival time in men was 8 months and in women 11 months, there was no statistically significant difference in the duration of survival between sex in a 5-year postoperative period (Fig. 6).

Table 3. Prognostic factors in group of patients with Long-Term Survivors ≥ 24 months (7 patients)

Characteristics	N	N	Percentage	χ^2	P
Male	71	5	7.0	0.05	NS
Female	34	2	5.9		
≤ 40 god	9	3	33.3	11.25	< 0.001
> 40 god	96	4	4.2		
Gr. III	69	6	8.7	13.3	< 0.024
Gr. IV	36	1	2.8		
RH therapy	14	3	21.4	5.66	< 0.017
R therapy	91	4	4.4		
RO	15	5	33.3	20.0	< 0.00001
O	90	2	2.2		

H – radiotherapy + chemotherapy
RO – repeated surgery

R – radiotherapy
O – only one times operated

NS – non significant

The group of patients who lived longer than 24 months deserved special attention, accepting them as a favorable prognostic group, where the difference in representation of men and women was not so significant (7.0 % men against 5.9 % women) (Table 3). Even one-third of those who

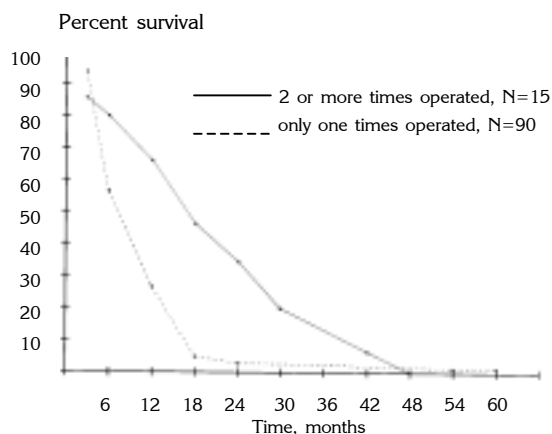


Fig. 5. Influence of number of operation on patients survival

were less than or equal to 40 years of age and one-third also those who had repeated surgery lived longer than 24 months. Over 20% of patients who were treated postoperatively by chemotherapy belong to this prognostic group and 85% patients in this group had Grade III tumors. A 49-years old male with a Grade III tumor having 6 courses of chemotherapy had the longest duration of life without repeated surgery.

Discussion

Although Netsky et al 1950(7) reported two patients who lived 7 and 14 years respectively after the operation of glioblastomas in the majority of other published papers the long term survival rate of patients operated on due to high grade astrocytomas were only as case reports (4,5,6,8). In a series of 399 high grade astrocytomas' patients Roth and Elvidge (16) reported 8.8 % survivors at 2 years, 5 % at three years and only 3 % at five years. Other published papers appearing later recorded a 5-year survival rate in only 0.8% (11).

The new diagnostic possibilities including not only early detection of these brain lesions but also a more scrupulous follow-up together with radiation and chemotherapy no doubt improved the survival rate of these patients. That may explain why case reports about patients with a 10-year period of survival increased (8,9). Salcman et al (1) multidisciplinary study published in 1994

deserves special attention.

In our series of 105 patients with malignant astrocytomas a two year survival rate was in 6.66 %, three year survival (the long term survival) was only 4.8 % and only one patient lived longer than 5 years.

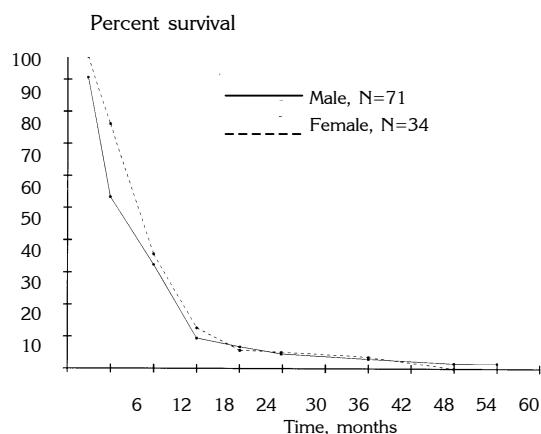


Fig. 6. Influence of sex on patients survival

It was pointed out that age (the most favorable results are in group of patients who were less than or equal to 40 years of age); the degree of malignancy; the chemotherapy and the repeated surgery were a statistically significant factor of survival rate.

Comparing our data with Salcman's et al (1) study a significant difference of survival rate is evident especially in the first year of establishing the histological diagnosis, where the mortality rate is twice as high than in Salcman's study. Regarding the fact that this period can be in connection with the radicality of the operation, the dose of radiation (the majority of authors reported that radiation was 60 Gy) and fitness for the cytostatic treatment one can draw the conclusion about the wrong type of treatment. Detailed analysis found that only 7 patients (8.5 %) were ≤ 40 in contrast to the Salcman's et al group where the figure was reached 30 %. The young age as a significant factor stressed also Rutz (8), and Hatanaka (10). On the other hand only 13.1 % of patients in our study received chemotherapy in contrast to 64.7 % of Salcman's et al (18) patients as well as 14.3 % repeated surgery cases against 70.6 % from the same source which speaks clearly in favor of our hypothesis about the significant factor of the survival time.

By analyzing patients who survived 24 months and longer one confirmed the striking influence of the above mentioned factors of survival where the younger age and the repeated surgery impose

themselves as the primary prognostic factors of survival (1). The local immunosuppressive affection of the high-grade astrocytomas was described earlier (9).

The increasing density of the immunocompetent host cells in the vicinity of high grade astrocytomas after reduction of the volume of the tumor and the total (whole) quantity of the tumors immunosuppressors demand that the repeated surgery must not be comprehended and reduced exclusively to the decompression.

Better information about the factors which

determine the biological potential of high grade astrocytomas and control immunological parameters which determine the rhythm of development of malignant process is the only way which can lead to successful therapy and strengthen life in those patients. In that sense special attention reports about the treatment of high grade astrocytomas by interleukin 4 (11), interferon β (12), interleukin 2 stimulated killer lymphocytes (13), the antagonist peptide such as somatostatin (14) deserve special attention.

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DUŽINA PREŽIVLJAVANJA U PACIJENATA SA VISOKOMALIGNIM ASTROCITOMIMA

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Sažetak: Retrospektivno su analizirani operativno tretirani astrocitomi III i IV stepena maligniteta, u periodu 1985–1989. godine. Praćena je dužina preživljavanja u petogodišnjem periodu. Validnu grupu činilo je 105 pacijenata. Analizom nije obuhvaćeno 16 pacijenata zbog uzrasta mlađeg od 18 godina, neposrednog postoperativnog umiranja usled kardio-pulmonalnih komplikacija, kao i nepotpune medicinske dokumentacije o postoperativnom lečenju i vremenu smrti. Od 105 pacijenata validne grupe, 69 je imalo tumor III stepena (65,7%), a 36 pacijenata tumor IV stepena. Muškaraca je bilo 71 (67,6%), žena 34. dominirali su stariji od 40 godina (91,4%), prema svega 9 pacijenata mlađih od 40 godina. U seriji je zabeleženo jednogodišnje preživljavanje u 1/3 pacijenata, dvogodišnje u 7 %, trogodišnje u 5 %, dok je 5 godina preživeo samo 1 pacijent. Duže preživljavanje je zabeleženo u pacijenata mlađih od 40 godina ($p < 0,001$), sa histološkim gradusom III ($p < 0,024$), hemiotretiranih ($p < 0,017$), odnosno reoperisanih pacijenata ($p < 0,00001$). Pol nije statistički značajno uticao na dužinu preživljavanja. Svi pacijenti su u sklopu iradijacione terapije tretirani sa 42 Gy, a njih 14 bilo je podvrgnuto hemioterapiji ($p < 0,017$). U grupi 15 reoperisanih pacijenata procentualno zastupljeniji bili su muškarci 12 (16,9%), pacijenti mlađi od 40 godina ($p < 0,087$), sa histološkim gradusom III ($p < 0,021$). Dužina preživljavanja posle reoperacije bila je 3–4 puta kraća nego posle prve operacije.

Zaključujemo da multidisciplinarni (neurohirurško-onkološki) pristup lečenju visokomalignih astrocitoma može doprineti dužem preživljavanju, ali se prave perspektive produženja života u takvih pacijenata očekuje tek primenom aktivne imunološke terapije.

Ključne reči: Astrocitomi, hemioterapija, reoperacije, preživljavanje

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