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<RH>Klekner, *et al*.: Survival of glioblastoma patients

Original Article

Influence of oncotherapy and clinical parameters on survival of glioblastoma patients: A single center experience

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ABSTRACT

Background: Routine administration of temozolomide (TMZ) in the treatment protocol of glioblastoma in the last few years resulted in improving survival parameters of these patients but efficacy of supplementary bevacizumab (BVC) monotherapy has not been evidently proven. In this study, the effectiveness of different postoperative therapy for glioblastoma patients treated in our institute was evaluated. In addition, the prognostic value of clinical parameters on survival was also analyzed.

Methods: Accordance of clinical parameters (age, gender, tumor localization, size, side, Karnofsky performance score, and extension of tumor removal), postoperative treatment (radiotherapy [RT], RT + TMZ, RT + TMZ + BVC), and survival data were tested by 104 patients operated on glioblastoma in the Department of Neurosurgery, University of Debrecen between 2002 and 2012.

Results: Concurrent chemo-RT resulted in significant longer overall survival (OS) than RT alone ($p_{RT \text{ vs. } RT + TMZ} = 0.0219$) and BVC treatment after progression during TMZ also elongated survival significantly ($p_{RT \text{ vs. } RT + TMZ + BVC} < 0.0001$; $p_{RT + TMZ \text{ vs. } RT + TMZ + BVC} = 0.0022$), respectively. Clinical parameters showed no significant influence on OS in comparison with different methods of postoperative oncotherapy.

Conclusions: Both TMZ and BVC had beneficial effect on glioblastoma patients' survival, but tested clinical parameters showed no evident accordance with final outcome. Although neurosurgery has an indispensable role in resecting space occupying tumors and providing good postoperative performance score patients for oncotherapy, the survival of glioblastoma patients depends rather on radio- and chemo-sensitivity than tested clinical parameters.

Key words: bevacizumab; glioblastoma; oncotherapy; surgery; survival

<H1>Introduction

Glioblastoma multiforme (GBM) is a malignant disease of the central nervous system with extremely poor prognosis. The overall survival (OS) rates in the literature with or without therapy are equally among the worst of all malignant tumors. The most novel treatment strategies provided 9.8% 5-year survival rate.[1] Estimated median OS of untreated patients is not longer than 3–6 months.[2]

The majority of the diagnosed patients is usually aged 45–65. Younger age is reported to associate with a better outcome, and male patients have a better prognosis compared to female ones (8.9 vs. 5.6 months).[3] Tumors show rapid growing, symptoms – which are dependent on location – present themselves early. Increased intracranial pressure often develops due to the space-occupying tumor. In general, only partial surgical removal is possible because excessive peritumoral infiltration hinders complete resection. The location and extent of the tumor are the main factors influencing the extension of resection. Multilobular localization is traditionally associated with very poor prognosis. Previous data show that low preoperative Karnofsky score, dominant hemisphere involvement, and larger tumor size are the factors decreasing survival rates.[4]

Radiotherapy (RT) was the only postoperative therapeutic procedure for glioblastoma patients for decades. Introducing RT to the neurosurgical treatment increased the OS rates from 3–6 months (expected survival without postoperative treatment) to 9–12 months.[5-9] Later on, temozolomide (TMZ) has been added to RT resulting yet another increase in survival rates: TMZ treatment increases both progression-free (4.5 vs. 6.9 months) and OS rates (8 vs. 14.6 months).[10-14] Concurrent chemo-irradiation is recently the routine baseline treatment modality for GBM patients.[15] Recently, vascular endothelial growth factor (VEGF) inhibitor bevacizumab (BVC) is one of the most widely used supplementary drugs either as a

supplementation to TMZ treatment or as a drug of second choice. Treatment with BVC may increase survival rates, however, data regarding OS are not convincing enough to draw final conclusions at the moment.[12,13,16]

Since treatment protocol of glioblastoma patients has undergone major changes in the past 7 years, there is a demand for the comprehension of treatment-dependent survival rates and reassessment of clinical and neurosurgical prognostic parameters affecting survival. In addition, it begs the question whether the use of systematic chemotherapeutic agents can change the expected extent of surgical removal. Evaluating the effect of postoperative oncotherapy, reconsideration of the prognostic relevance of certain clinical parameters, including radicality of the surgery might be important for neurosurgeons.

At the Department of Neurosurgery, University of Debrecen, routine use of concurrent chemo-irradiation with TMZ for GBM was introduced in 2006. BVC monotherapy in recurring tumor after concurrent chemo-irradiation and TMZ monotherapy was administered in 2009. In this study, we analyze the efficacy of various treatment modalities (irradiation, concurrent chemo-irradiation, and supplement BVC therapy), and the role of clinical parameters affecting survival in our patients will be also evaluated.

<H1>Methods

In this study, 104 patients who underwent neurosurgery due to GBM between 2002 and 2012 were included. Only those patients were selected for this study whose full medical history was available and whose follow-up was complete. The 104 patients were classified into the five following groups:

1. Best supportive care (BSC) group: 15 patients not receiving postoperative radio- or chemo-therapy due to very poor Karnofsky performance score (KPS) create this

group .

2. Palliative RT (pRT) group: consists of 9 patients who received only pRT after surgery (10 × 3 Gy) – based on their KPS score being <60 (pRT-group).

3. RT-group: 20 patients belong to this group operated between 2002 and 2005. They received full dose whole brain RT without any chemotherapy (30 × 2 Gy focal brain RT).

4. RT + TMZ group: Patients operated after 2006 received combined radio-chemotherapy after surgery, that is, 30 × 2 Gy focal brain RT + concurrent TMZ + 6–12 cycles TMZ monotherapy depending on progression. This group includes 35 cases.

5. BVC group: This group contains 25 patients who received BVC due to recurrence of glioblastoma after the concurrent chemo-irradiation (see group 4). However, as BVC therapy in the treatment of glioblastoma was introduced in Hungary in 2009, those patients whose disease progressed before 2009 could not receive BVC.

During the procession of data, clinical parameters such age, gender, tumor side, localization and the longest diameter of tumor, pre- and post-operative KPS, and radicality of surgical intervention were analyzed. Surgical intervention was evaluated as (1) biopsy, (2) partial resection, and (3) macroscopically total resection. The extent of resection was confirmed by using computer tomography with contrast material performed within 24 h after surgery. This method was suitable for deciding if the surgery was macroscopically total or not. After the first surgery, each patient underwent regular follow-up magnetic resonance imaging (MRI) examinations every 3 months.

In case of evident clinical deterioration (determined as the major neurological deficit and

Karnofsky score <60) and inoperative progrediating tumor recurrence, intravenous methyl-prednisolon was administered to each patient as salvage therapy.

The effectiveness of the various treatment methods and the connection of the clinical parameters on survival were tested.

During the statistical analysis, we recognized a definitely great deviation in OS in case of patients receiving adjuvant radio-and chemotherapy (median survival time: 16.5 ± 13.3 months). To determine the reason of the difference in survival time in spite of the similar neuro-oncotherapy, clinical parameters were compared between two groups of patients: "group A" contained the patients with an OS time of less than the median survival time (OS <16 months). "Group B" was formed by patients with an OS of more than 16 months (OS ≥16 months).

<H2>Statistical analysis

For statistical analysis, paired sample *t*-test and Mann–Whitney tests were used to check the significance of difference between pre- and post-operative KPS, progression-free survival (PFS), postprogression survival (PPS) and OS. Age, gender, side of tumor, various surgical interventions, and tumor location in the two different survival groups were measured by comparison of ratios. Survival curves were created with Kaplan–Meier analyses, the difference of curves was tested with log-rank test. During our statistical analysis, 5% of significance level was used.

<H1>Results

<H2>Progression-free and overall survival

Progression-free, postprogression, and OS of patients in different treatment groups, was

determined [Figure 1]. About 20% increase in volume or a new tumor on MRI scans was accepted as progression. The median PFS in BSC group was 1.4 ± 1.4 months. In case of the patients who received only palliative dose of irradiation (pRT), the result was 1.1 ± 0.4 months. In patients receiving full dose RT, the PFS was 4.7 ± 4.7 months. PFS in the combined RT + TMZ treatment group was 7.4 ± 5.5 months; while in the BVC group, the time until first progression was 11.8 ± 8.5 months. In the same group, the time until the next progression (after starting BVC therapy) was 8.5 ± 5.4 months.

PPS also gives information about the effectiveness of therapy. The BSC patients had a median PPS of 2.3 ± 3.7 months, PPS of pRT patients was 3.1 ± 3.9 months. The PPS in the RT group was 4.4 ± 5.8 months while it was 7.9 ± 7.6 months in the RT + TMZ group. In the BVC group, the PPS after the first progression was 11.1 ± 5.8 months.

Statistically, TMZ (RT + TMZ) has significantly increased the PFS compared to RT, which survival has been increased further by BVC ($p_{[RT\ vs.\ RT + TMZ]} = 0.009$ and $p_{[RT + TMZ\ vs.\ BVC]} = 0.0232$). On the other hand, we can state that the pRT had no significant effect on patients' survival ($p_{[BSC\ vs.\ pRT]} = 0.718$).

Median OS after diagnosis in the different treatment modality groups was 3.7 ± 4.3 months in the case of BSC patients and 4.2 ± 3.9 months in pRT-group. Kaplan–Meier survival analysis of these two groups did not show any significant difference ($P < 0.364$). OS of patients in the RT-group was 9.1 ± 8.7. RT + TMZ patients had an OS of 15.3 ± 9.5 months while BVC-group had the longest OS: 22.9 ± 8.6 months. Kaplan–Meier survival analysis showed that the survival distribution differs significantly in among these three groups [$P < 0.0005$, Figure 2].

After analyzing the effectiveness of different treatment methods on survival, clinical parameters of patients were also tested. Clinical data are summarized in Table 1. Results are detailed below.

<H2>Age

There was no significant difference in the age of patients testing the different groups by postoperative therapy (BSC = 66.1 ± 10.3 years; pRT = 65.6 ± 18.9 years; RT = 63.7 ± 8.5 years; RT + TMZ = 51.8 ± 13.5 years; BVC = 55.2 ± 9.6 years).

<H2>Gender

By testing the proportions of gender in the different groups of treatment, the only significant difference was found in the case of the high ratio of males in the pRT group. Ratios of male patients in various treatment groups are the following: BSC: 53%, pRT: 78%, RT: 45%, RT + TMZ 58%, BVC: 52%.

<H2>Side of tumor

In the BSC-group, 47% of the patients had left sided tumor while in the pRT-group, it is 56% of the patients. About 55% of tumors were in the left hemisphere in the RT-group and 54% in the RT + TMZ group. About 56% of tumors were left sided in the BVC group. About 23% of tumors were bilateral in the BSC group and 9% in the RT + TMZ group at the time of diagnosis. There were no bilateral tumors in the other groups. None of the groups had a significant difference in laterality.

<H2>Karnofsky performance score

In our research, the median preoperative and postoperative Karnofsky score of the RT + TMZ group was 77.7 and 80.3, respectively. The change in KPS score was very similar to this in the BVC group as well: The KPS raised from preoperative 76.0 to postoperative 80.8. The median Karnofsky score did not change significantly in the RT group either it was 72.0 before or 72.4 after surgery. On the other hand, the preoperative KPS in the pRT group was 62.2 and 61.1 postoperatively. The KPS also dropped in the BSC group, from preoperative 70.1–56.0

after surgery.

The preoperative Karnofsky scores of pRT group was significantly lower than the ones of RT + TMZ and BVC ($p_{[pRT\ vs.\ RT + TMZ]} = 0.029$, $p_{[pRT\ vs.\ BVC]} = 0.003$). However, postoperative KPS of the BSC group was significantly lower compared to other groups, except the pRT group ($p_{[BSC\ vs.\ pRT]} = 0.6096$, $p_{[BSC\ vs.\ RT]} = 0.0162$, $p_{[BSC\ vs.\ RT + TMZ]} = 0.0014$, $p_{[BSC\ vs.\ BVC]} = 0.001$). In addition, postoperative KPS of patients receiving RT alone were significantly lower compared to patients receiving concurrent chemo- RT (RT + TMZ) ($p_{[RT\ vs.\ RT + TMZ]} = 0.0131$). The postoperative KPS score of BVC group was significantly higher than those of RT and pRT group ($p_{[pRT\ vs.\ BVC]} = 0.035$, $p_{[RT\ vs.\ BVC]} = 0.013$).

<H2>Size of tumor

Median of maximal tumor diameters measured on contrast-enhanced MRI in the five groups were: 4.9 ± 1.3 cm (BSC), 4.8 ± 1.7 cm (pRT), 4.3 ± 1.5 cm (RT), 4.1 ± 0.9 cm (RT + TMZ), and 4.2 ± 1.3 cm (BVC). Statistical analysis proved no significant difference in the various postoperative treatment groups regarding the size of tumor.

Evaluation of OS in connection to tumor size at the time of diagnosis, the following results could be determined. OS of patients with tumor under 4.0 cm of size was 9.6 ± 10.6 months in the RT group, 15.9 ± 9.1 months in the RT + TMZ group, and 24.8 ± 7.6 months in the BVC group. OS of patients with tumor >4.0 cm was 8.4 ± 5.6 months in the RT group, 14.9 ± 9.7 months in the RT + TMZ, and 21.7 ± 9.3 for patients in BVC group.

We found that tumor size had no significant effect on survival of patients in any of the different oncotherapeutic group, even though patients with smaller tumor had somewhat better results, these differences were not proven to be significant (*P* values of the various oncotherapeutic groups, tumor size ≤4.0 cm vs. tumor size >4.0 cm: $p_{RT} = 0.782$, $p_{RT + TMZ} = 0.559$, $p_{BVC} = 0.395$) [Figure 3].

<H2>Type of surgery

Figure 4 shows how various types of surgical interventions split among patients in the five treatment groups. The proportion of biopsy in the RT + TMZ group is significantly lower than in the BSC group ($p = 0.039$), pRT group ($p = 0.004$), and RT group ($p = 0.039$). However, there is no significant difference in the proportion of biopsies compared BSC to BVC ($P = 0.184$). It is important to note that the proportion of radical and partial surgeries in the oncotherapeutic groups (RT, RT + TMZ, BVC) is similar ($p_{[RT\ vs.\ RT + TMZ]} = 0.268$, $p_{[RT\ vs.\ BVC]} = 0.266$, $p_{[RT + TMZ\ vs.\ BVC]} = 0.725$).

Results of survival rates regarding various surgical interventions are shown in Figure 5. In cases when only biopsy was performed, RT provided an OS of 8.2 ± 5.7 months, whereas with combined chemo-RT patients lived only for 4.0 ± 0.8 months. In case of partial tumor resections with RT, OS was 9.8 ± 8.9 months, 13.9 ± 6.8 months with RT + TMZ ($p_{[RT\ vs.\ RT + TMZ]} = 0.388$). Radical tumor resection combined with RT alone results in an OS of 9.3 ± 10.3 months. Radical resection plus RT + TMZ treatment leads to a median survival of 16.6 ± 10.8 months ($p_{[RT\ vs.\ RT + TMZ]} = 0.067$). OS in the BVC group is 23.5 ± 11.1 months with partial resection and 23.8 ± 5.9 months with radical resection. The OS in BVC group significantly increases in both cases of partial and radical surgeries compared to RT + TMZ ($p_{[part.\ RT + TMZ\ vs.\ part.\ BVC]} = 0.023$ and $p_{[radic.\ RT + TMZ\ vs.\ radic.\ BVC]} = 0.017$). There is no significant difference between the survival of patients who undergo partial and radical surgery in the same treatment group ($p_{[part.\ RT + TMZ\ vs.\ radic.\ RT + TMZ]} = 0.413$ and $p_{[part.\ BVC\ vs.\ radic.\ BVC]} = 0.926$).

<H1>Discussion

Primary brain tumors are one of the leading causes of death because of cancer. The incidence of glioblastoma in the United States is 10–12:100,000/year, it is 1.5 times more frequent in males than in females. It is most common in 40–65 years old people, with the median of 54

years.[17,18] Gliomas are accountable for 30–40% of all intracranial tumors. More than half of the gliomas (approximately 65%) are glioblastoma in adults. Thus, it is the most common high-grade glioma and the most common intracranial malignant tumor.[19,20]

Successful treatment of glioblastoma is a great challenge for neuro-oncologists all over the world. The first step of treatment of newly diagnosed glioblastoma is the resection of the tumor, if possible. Complete eradication is practically not achievable due to the aggressive invasiveness of the tumor. It means glioma cells remain back in the surrounding area even if resection was made with tumor-free boundaries, so sooner or later relapse of the disease appears. In addition, in case of multifocal tumors or tumors affecting the corpus callosum or eloquent regions surgical intervention usually means biopsy.[21]

In general, surgery is followed by RT, where the irradiated volume includes a 2–3 cm wide safety zone in the tumor-free tissue. RT is delivered in 1.8–2 Gy fractions up to a total dose of 54–60 Gy over 6 weeks. Based on the results of the Stupp-study in 2005, adjuvant chemotherapy (75 mg/m^2/day TMZ) concurrently with RT has become the standard therapy for patients under 70 years who has good KPS score. This is followed by TMZ monotherapy (at least 6 cycles of 150–200 mg/m^2/day over 6 months, 5 days a month).[14] The alkylating agent TMZ was reported to increase significantly both progression-free and OS. The therapeutic benefits are more expressed when hypermethylation of the MGMT region is present in the DNA of tumor cells.[22,23]

Treatment could be continued with BVC monotherapy after tumor progression during TMZ treatment. BVC is a monoclonal humanized antibody made against VEGF-A. Glioblastoma is a highly vascularized tumor, using high amount of VEGF and other pro-angiogenic factors for neovascularization.[13] At the beginning, it was used for recurring GBM only, lately, however, researchers and clinicians have found therapeutic benefits of using BVC in primary treatment,

too. Numerous studies have evaluated and demonstrated the antitumor effect of BVC. The conclusion of these studies is that BVC has no significant effect on OS even though it does increase PFS significantly.[13,24-26]

We have studied the full history of 104 patients treated with glioblastoma between 2002 and 2012 and efficiency of different treatment methods and the possible prognostic role of certain clinical parameters have been analyzed.

Evaluating the effectiveness of different treatment modalities, namely BSC, decreased dose of irradiation (pRT), full dose RT, concurrent chemo-RT (RT + TMZ) and supplementary BVC treatment after progression (BVC) regarding survival results were analyzed. We found that pRT has no significant effect on PFS; in addition, it barely improved OS compared to BSC. Because the effect of pRT on survival elongates mostly the poor postprogression neurologic status of patients, its effectiveness is doubtful.

Both progression-free and OS of patients receiving full dose RT were significantly increased compared to BSC or pRT, just as concurrent RT + TMZ treatment has significantly increased survival data in comparison to RT alone. BVC monotherapy following concurrent chemo-RT further increased the survival compared to other groups. Taking a closer look on the data of BVC group and comparing them to the results of patients receiving concurrent chemo-irradiation (RT + TMZ); however, the difference is not absolutely evident. PFS of RT + TMZ and BVC patients is 7.4 months and 11.8 months, respectively, and the 4.4 months difference between the two results decreases the difference between the OS of these groups (OS of RT + TMZ = 15.3 ± 9.5; BVC = 22.9 ± 8.6) to 3.2 months instead of 7.6 months. This 3.2 months difference in survival is statistically not significant. The difference in the PFS may be the result of the selection of patients that are candidates for BVC monotherapy based on their good KPS after tumor progression. Thus, this patient selection bears some advantage for

patients whose disease progresses slower and reacts probably better to chemotherapy. So, even though patients who received BVC clearly had longer OS than those who did not get the treatment, the difference cannot be supported with statistical analysis.

Regarding clinical parameters, it could be established that the gender and age of the patient, the side, size, and location of the tumor cannot be used as an independent prognostic factor. The radicality of surgical removal in case of postoperative concurrent chemo-RT (RT + TMZ group) seemingly had a positive effect on survival [Figure 5], but this connection could not be confirmed statistically. ($p_{[\text{part. RT + TMZ vs. radic. RT + TMZ}]} = 0.429$ and $p_{[\text{part. BVC vs. radic. BVC}]} = 0.926$). These kind of investigations has been already reported but with various conclusions in the corresponding literature.[9,27-30]

Furthermore, the size of the tumor had no statistically proven effect on survival of patient neither in the RT only nor in the RT + TMZ group although patients with smaller tumors had slightly better survival. However, this difference may be due to the increased risk of surgery caused by the larger size of tumor. Our results suggest that chemotherapy and RT exert their clinical effect independently of tumor size. Back *et al*. have come to the same conclusion in their study.[31] It is also reported that tumor size larger than 4 cm is a negative prognostic factor especially in case of old patients (average 73 ± 5 years), which significantly decreases average OS.[27] Similarly, Donato *et al*. described that survival of glioblastoma patients is dependent on various factors that are independent of each other, but they have a complex effect on survival together. One of these factors is tumor size and tumor size larger than 4 cm is a negative prognostic marker.[28] Based on our results, we think that tumor size alone is not an absolutely negative prognostic marker since chemosensitive tumors can react well to oncotherapy independently of tumor diameters. On the other hand, tumor size really means an evident risk factor regarding surgical removal, and it can decrease survival chances due to the

obscure postoperative KPS. Since postoperative KPS and the neurological status of the patient have a direct effect on the indication of postoperative treatment, preservation of good postoperative status is more important for a better prognosis than radical excision. Therefore, in case of tumors in high-risk location only partial resection should be suggested.

<H2>Analyzing results of patients receiving the same basis-therapy

From the 104 patient in this study, we selected patients who received radio- and chemo-therapy after the surgical intervention. Sixty patients met to the selection criteria. The KPS of these patients was at least 70, all of them received 60 Gy focal brain RT with concurrent TMZ treatment prolonged with at least two cycles monotherapy until progression (deterioration of neurologic status or tumor progression proven by MRI). In spite of the same basis-therapy of these patients, OS (16.5 ± 13.3 months) had an extremely wide range from 4 to 43 months. To find the reason behind the difference of survival, patients were separated in two groups. Patients with an OS under the median 16 months belonged to group A (OS = 10.2 ± 4.2 months) while patients who survived more than 16 months formed group B (OS = 25.7 ± 7.4). Comparison of clinical parameters of group A and B was made to find the possible clinical explanation to the great difference in survival and to find eventual clinical prognostic factors. Clinical data of the two groups are summarized in Table 2a-c.

After comparing the data of the two groups, it could be established, that the proportion of gender, the median age of patients, the side, size and the location of the tumor, the pre- and post-operative Karnofsky score did not differ significantly. Significant difference was proven in case of the survival data which was set as a selection parameter (PFS = 4.5 ± 2.3 months vs. 13.4 ± 7.5 months, $p < 0.0001$, OS = 10.2 ± 4.2 vs. 25.7 ± 7.4, $p < 0.0001$). Analysis of Kaplan–Meier survival curves also shows a significant difference between group A and group B [$p < 0.0005$, Figure 6].

The proportion of radical tumor resection was slightly greater in group B (62.5% vs. 50.0%), where survival was a little bit longer but the difference in proportions is not statistically significant (P = 0.475). We also tested the ratio of reoperations in group A and B and found no statistically significant difference. In addition, OS of patients who had more than one operation was not found to be significantly longer from those who had a single operation [p = 0.13, Figure 7]. Beside this, survival curves by Kaplan–Meier analysis and the cumulative OS did not differ among patients with different types of surgeries [p = 0.416, Figure 8].

<H1>Conclusions

Based on these results, it can conclude that the survival of patients is in general not affected by the clinical parameters, but the chemo- and radio-sensitivity of the tumor. Neurosurgeons may increase the chance for survival with the extension of tumor resections, however, when this reaches its limits then the effectiveness of treatment depends mainly on the method of oncotherapy and the chemo- and radio-sensitivity of the tumor. Predicting the chemosensitivity of glioblastoma to different anticancer agents and determining relevant genetic prognostic factors is a matter of molecular pathology.

<H1>References

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Tables

Table 1: Clinical parameters of 104 patients who underwent surgery due to glioblastoma

Treatment group	Number of cases	Mean of age (years)	Mean of size (cm)	Mean of preoperative KPS	Mean of postoperative KPS	Gender of patients	Side of tumor	Mean of PFS (months)	Mean of OS (months)
BSC	15	66.1±10.3	4.9±1.3	70.1±14.6	56.0±23.5	Male:	Left:	1.4±1.4	3.7±4.3
pRT	9	65.6±18.8	4.8±1.7	62.2±12.0	61.1±23.1	Male:	Left:	1.1±0.4	4.2±3.9
RT	20	63.7±8.5	4.3±1.5	72.0±13.2	72.4±13.6	Male:	Left:	4.7±4.7	9.1±8.7
RT + TMZ	35	51.8±13.5	4.1±0.9	77.7±19.6	80.3±10.1	Male:	Left:	7.4±5.5	15.3±9.5
BVC	25	55.2±9.6	4.2±1.3	76.0±10.8	80.8±9.1	Male:	Left:	11.8±8.5	22.9±8.6

BSC - Best supportive care, pRT - Palliative radiotherapy, RT - Radiotherapy, RT + TMZ - Radiotherapy with concurrent temozolomide chemotherapy, BVC - Concurrent chemo-radiotherapy supplemented with bevacizumab after progression, KPS - Karnofsky performance score, PFS - Progression-free survival, OS - Overall survival

Table 2a: Clinical parameters of groups of patients with same basis-oncotherapy but different overall survival

Survival group	No. of cases	No. of patients receiving BVC	No. of reope-rated patients	OS (months)	PFS (months)	Gender (male/ female)	Age (years)	Side (right/ left)	Preop. KPS	Postop. KPS	Size of tumor (cm)
Group A	28	7	7	10.2 ±4.2	4.5 ±2.3	15/13	52.0 ±13.2	16/ 12	75.4 ±19.3	77.5 ±8.0	4.3 ±1.0
Group B	32	18	15	25.7 ±7.4	13.4 ±7.5	19/13	54.3 ±11.0	11/ 21	78.4 ±13.5	78.4 ±10.3	4.1 ±1.1

BVC – bevacizumab, KPS - Karnofsky performance score, PFS - Progression-free survival, OS - Overall survival

Table 2b: Location of tumors of patients with same basis-oncotherapy but different survival

Tumor location	Frontal	Temporal	Parietal	Occipital	Multilobular
Group A	11	3	4	1	9
Group B	8	11	5	2	6

Table 2c: Distribution of various types of surgeries among patients

Type of surgery	Biopsy	Partial	Radical
Group A	4	10	14
Group B	1	11	20

Figure Legends

Figure 1: Survival of patients treated with various treatment modalities. BSC - basic supportive care, pRT - Palliative radiotherapy, RT - Radiotherapy, RT + TMZ - Radiotherapy with concurrent temozolomide chemotherapy, BVC - Radiotherapy with concurrent temozolomide chemotherapy supplemented with bevacizumab after progression

Figure 2: Kaplan–Meier survival analysis and survival distribution of patients in RT, RT + TMZ and BVC group. RT - Radiotherapy, RT + TMZ - Radiotherapy with concurrent temozolomide chemotherapy, BVC - Radiotherapy with concurrent temozolomide chemotherapy supplemented with bevacizumab after progression

Figure 3: Overall survival of glioblastoma patients in connection to tumor size and treatment modalities. BSC - Basic supportive care, RT - Radiotherapy, RT + TMZ - Radiotherapy with concurrent temozolomide chemotherapy, BVC - Radiotherapy with concurrent temozolomide chemotherapy supplemented with bevacizumab after progression

Figure 4: Proportions of various surgical interventions in different postoperative treatment groups. BSC - Basic supportive care, RT - Radiotherapy, RT + TMZ - Radiotherapy with concurrent temozolomide chemotherapy, BVC - Radiotherapy with concurrent temozolomide chemotherapy supplemented with bevacizumab after progression

Figure 5: Overall survival after the different extent of tumor removal and various treatment modalities in glioblastoma patients. RT - Radiotherapy, RT + TMZ - Radiotherapy with concurrent temozolomide chemotherapy, BVC - Radiotherapy with concurrent temozolomide chemotherapy supplemented with bevacizumab after progression

Figure 6: Kaplan–Meier survival analysis and survival distribution of patients in group A and group B

Figure 7: Kaplan–Meier survival analysis and survival distribution of patients receiving the same basis-therapy in connection to number of operations

Figure 8: Kaplan–Meier survival analysis and survival of patients receiving the same basis-therapy in connection various surgical intervention