Butterfly Glioblastoma - the Impact of Tumor Volumes and Treatment Strategies on Clinical Outcome

Line Sagerup Bjorland (line.bjorland@sus.no)
Stavanger University Hospital: Department of Oncology https://orcid.org/0000-0003-3043-7804
Kathinka Dæhli Kurz
Stavanger University Hospital: Department of Radiology
Fluge Øystein Fluge
Haukeland University Hospital: Department of Oncology and Medical Physics
Bjørnar Gilje
Stavanger University Hospital: Department of Oncology
Rupavathana Mahesparan
Haukeland University Hospital: Department of Neurosurgery
Hege Sætran
Haukeland University Hospital: Department of Pathology
Anastasia Ushakova
Stavanger University Hospital: Department of Research, Section of Biostatistics
Elisabeth Farbu
Stavanger University Hospital: Department of Neurology

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Abstract

Purpose

Butterfly glioblastoma is a rare subgroup of glioblastoma with a bihemispheric tumor crossing the corpus callosum, and is associated with a dismal prognosis. Prognostic factors are previously sparsely described and optimal treatment approaches remain uncertain. We aimed to analyse prognostic factors in butterfly glioblastoma, and to evaluate treatment strategies and outcome in a real-world setting.

Methods

We conducted a retrospective population-based cohort study of patients diagnosed with butterfly glioblastoma in Western Norway between 01/01/2007 and 31/12/2014. Clinical data were extracted from electronic medical records. Molecular and MRI volumetric analyses were retrospectively performed. Survival analyses were performed using Kaplan-Meier method and Cox proportional hazards regression models.

Results

Among 381 patients diagnosed with glioblastoma, 36 patients (9.4%) met the criteria for butterfly glioblastoma. Median overall survival was 5.9 months (95% CI 2.7-9.2) and three-year survival was 8.3%. Age was strongly associated with poorer outcome, with adjusted hazard ratio (HR) 1.06 (95% CI 1.03-1.10), p<0.001. Best supportive care was associated with poorer survival compared to multimodal treatment (adjusted HR 5.69 (95% CI 1.39-23.38), p=0.02).

Conclusion

Outcome from butterfly glioblastoma was dismal, with a median overall survival of less than six months. However, long-term survival was comparable to that observed in glioblastoma in general, and multimodal treatment was associated with longer survival. This suggests that patients with butterfly glioblastoma may benefit from a more aggressive treatment approach despite the overall poor prognosis.

Introduction

Butterfly glioblastoma is a subgroup of glioblastoma where tumor crosses the corpus callosum and affects both hemispheres [1, 2]. Previous studies have reported diverging incidence rates, ranging from 2.2 to 14.3% of adults diagnosed with glioblastoma [3-5]. It has been suggested that butterfly glioblastoma is clinically distinct from non-butterfly glioblastoma, being associated with less aggressive treatment, larger tumor volumes, and a poorer outcome [3]. It is uncertain whether the poorer prognosis is a consequence of intrinsic tumor features or due to the choice of treatment strategies. Improved knowledge on prognostic factors and treatment, and their impact on outcome, is required to enhance clinical decision-making. Few previous publications have described the treatment and outcome of butterfly glioblastoma [3-8]. The optimal treatment approach remains an unresolved concern, as it is

uncertain if results from studies on glioblastoma in general are applicable to this subgroup. A few studies have suggested a benefit from an aggressive treatment approach despite the poor prognosis [3, 4, 8]. There is no definitive consensus on recurrent glioblastoma treatment [9]. To the best of our knowledge, treatment of recurrent butterfly glioblastoma has not been described previously.

O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation and Isocitrate Dehydrogenase (IDH) mutations are favourable prognostic factors in glioblastoma [10, 11]. BRAF mutations are uncommon, but regularly seen in epithelioid glioblastoma [12]. Molecular characteristics of butterfly glioblastoma have only been described in small subsets in a few studies, and their prognostic values in this subgroup are not clarified [4, 8]. Due to the deep-seated tumor location of butterfly glioblastoma, MRI may serve as a useful non-invasive prognostic tool and help to determine the preferred treatment strategy. A few previous studies have described MRI volumetric analyses in butterfly glioblastoma [3-6]. Associations between tumor volumes and age, molecular subgroups and outcome has not been previously evaluated.

We aimed to evaluate the prognostic values of clinical, molecular, and radiological characteristics, including volumetric analyses of T1-weighted and T2-weighted and/or fluid attenuated inversion recovery (FLAIR) MRI, and to identify real-world treatment strategies and outcome from butterfly glioblastoma.

Methods

Design and sample

We conducted a population-based, retrospective cohort study with a follow-up of seven years, or until death. We identified all patients diagnosed with glioblastoma in Rogaland and Vestland counties of Western Norway, including ten secondary and tertiary referral centres, between 01/01/2007 and 31/12/2014. They included patients with histologically confirmed glioblastoma and those where the diagnosis was based on typical MRI pattern only, and where differential diagnoses were considered highly unlikely. We defined butterfly tumor as a contrast-enhancing tumor crossing the corpus callosum and affecting both hemispheres, corresponding to comparable studies [3, 4, 8]. Patients diagnosed with glioblastoma and with an MRI pattern meeting the butterfly tumor criteria were eligible for inclusion.

Measures

Patient characteristics and clinical findings were extracted from electronic health records (table 1). In cases where it was not documented, Karnofsky Performance Status (KPS) was retrospectively determined based on information in health records. Comorbidity burden was retrospectively assessed using Charlson comorbidity score [13].

Histological samples were re-evaluated by a neuropathologist. Molecular analyses were retrospectively performed on primary tissue samples. O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation was analysed using methylation-specific polymerase chain reaction (MSP) as a qualitative

method [14]. Determination of Isocitrate Dehydrogenase (IDH) mutational status was restricted to identification of the most frequent mutation, IDH1 R132H, and detected by immunohistochemistry with an IDH1 R132H specific monoclonal antibody. Identification of BRAF mutational status was restricted to mutation of codon 600 of exon 15 (V600E), being the most frequent activating mutation of the BRAF gene. Sanger DNA sequencing of exon 15, sequencing both the forward and the reverse strand, was performed.

MR images at time of diagnosis were re-evaluated by a neuroradiologist. Images were acquired from four different hospitals over an eight-year period, and imaging protocols varied regarding sequences and quality. T1-weighted series prior to, and after, intravenous gadolinium containing contrast agent, and T2-weighted and/or FLAIR series were present in all patients. Tumor characteristics were identified (table 1). Main location was defined as the lobe/region mainly affected by tumor. Involvement of the corpus callosum was classified according to Highley and colleagues [15]. Mass effect was measured as millimetres (mm) midline shift, and was classified as slight or severe with a cut off value of 10 mm, in line with a comparable study [16]. Contrast-enhancing tumor on T1-weighted series and tumor associated non-enhancing hyperintense lesions on T2-weighted/FLAIR series were identified, according to standardized neuro-oncological tumor assessment [17]. Volumes were delineated using the open source software platform 3D slicer Version 4.10.1, and measured in cubic centimetres (cm^3). Necrosis was included in the T1 volumes, and T1 volumes were included in the T2/FLAIR volumes.

Treatment and complications in primary and recurrence situations were registered (table 2). As discontinuation of, or changes in, treatment is a frequent concern, the completion of radiation therapy (60 Gy in 2 Gy fractions) with concurrent Temozolomide (TMZ) administered daily during the entire period, and the completion of at least one of six planned TMZ monotherapy courses, was classified as treatment according to the Stupp protocol [18]. All other combinations of radiation therapy and/or TMZ were classified as less-intensive chemoradiotherapy. Time of diagnosis was defined as the date of the first MRI, and progressive disease as unequivocal clinical or radiological progression. Long-term survival was defined as survival of three years or more, in line with previous studies [19, 20].

Statistics

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 16, and figures were created in R Version 4.0.4. Categorical data were presented as counts and percentages, and the between-group differences were assessed using Chi square (χ^2) and Fisher´s exact test, as appropriate. Continuous variables were presented as mean ± standard deviation (SD) or median and range or interquartile range (IQR). Comparison of two and multiple groups were performed using Mann-Whitney U and Kruskal-Wallis test, respectively. Correlations between continuous variables were assessed using Pearson correlation test, and presented as Pearson correlation coefficient (r). Survival analyses were performed using Kaplan-Meier plots and Cox proportional hazards regression models. To investigate the relations between patient characteristics and survival, we applied an unadjusted Cox model and a Cox

model adjusted for age and sex. No correction for multiple comparison was made. P values < 0.05 were considered statistically significant.

Results

We identified 381 patients diagnosed with glioblastoma in the study period. This cohort was described in a previous study [21]. Forty patients had a bihemispheric tumor crossing the corpus callosum. Three patients diagnosed by computed tomography (CT) only and one not meeting the histopathological criteria for glioblastoma were excluded. Finally, 36 patients (9.4% of patients diagnosed with glioblastoma) met the criteria for butterfly glioblastoma and were enrolled. One patient had previously received radiation therapy of the brain because of a low-grade astrocytoma. Median age was 65.9 years (range 27.9-84.8) and median Karnofsky Performance Status was 80 (range 20-100). Patient characteristics are listed in table 1.

Glioblastoma was histologically confirmed in 16 patients (44.4 %), for the remaining 20 patients (55.6%) the diagnosis was based on MRI pattern only. The latter group included two patients with non-representative biopsies. Among the 16 patients with conclusive biopsies, 14 samples were available for further analyses. Radiological, histopathological, and molecular characteristics are presented in table 1. IDH1 mutation was detected in three of 14 samples (21.4%), all of them in patients aged under 50 years. Nineteen patients (52.8%) presented with a midline shift, mean 7.9 mm (SD ± 3.1) and with a severe midline shift of 10 mm or more in five patients.

(Table 1 approximately here)

Median contrast-enhancing tumor volume in T1-weighted images was 40 cm^3 (range 2-146). Median volume of non-enhancing hyperintense lesions in T2-weighted/FLAIR images was 159 cm^3 (range 25-359). The ratio between T2/FLAIR and T1 volumes ranged from 1.1 to 119.7. Tumor volumes and location are shown in figure 1. There was no difference in median T1 volume between different locations (p=0.247). T2/FLAIR volumes were largest in frontal and temporal tumors with median volumes of 255 cm^3 (IQR 132-322) and 204 cm^3 (IQR 170-237), p=0.045.

(Figure 1 approximately here)

Both median T1 tumor volume and median abnormal T2/FLAIR volume were larger in the resection group than in the non-resection group: 105 cm^3 vs 38 cm^3 (p=0.03) and 277 cm^3 vs 121 cm^3 (p=0.01). All four patients with the largest T1 volumes (≥100 cm^3), and four of five patients with the largest T2 lesions (≥300 cm^3), were aged under 70 years. There was a slight trend towards larger T1 and T2 volumes in younger patients, however without statistically significant correlations (r= -0.226 (p=0.19) and r=-0.147 (p=0.39)).

Treatment and survival

Treatment and complications are outlined in table 2. Among patients aged under 70 years, 22 of 23 (95.7%) received radiation therapy, compared to eight of 13 patients (61.5%) aged over 70 years (p=0.02). Among patients aged under 70 years, 21 of 23 (91.3%) received multimodal treatment, compared to two of 13 patients (15.4%) aged over 70 years (p<0.0001). Hypofractionated radiation therapy was planned in four of six patients treated with best supportive care, but cancelled because of a rapid clinical deterioration.

(Table 2 approximately here)

Median overall survival was 5.9 months (95% CI 2.7-9.2), and median progression-free survival 4.0 months (95% CI 3.2-4.9). One-, two-, three-, and five-year survival rates were 19.4%, 16.7%, 8.3%, and 5.6%, respectively. Median survival in patients treated according to the Stupp protocol was 8.0 months (95% CI 7.5-8.5), compared to 5.5 months (95% CI 0.8-10.3) and 1.6 months (95% CI 0.5-2.6) in patients treated with less-intensive chemoradiotherapy and best supportive care (p<0.0001). Median survival in patients aged over 70 years was 2.1 months (95% CI 0.0-5.0), compared to 7.8 months (95% CI 6.4-9.2 months) in patients aged under 70 years (p<0.001). Nine patients (25.0%) died within three months of diagnosis. Survival curves are presented in figure 2.

(Figure 2 approximately here)

Older age and mainly deep-seated tumor location was associated with poor survival according to Cox regression adjusted for age and sex, with HR 1.06 (p<0.001) and HR 5.24 (p=0.01), respectively. Further, there was a slight association between larger T2/FLAIR volume and poorer outcome (HR 1.004, p=0.04). Best supportive care was associated with poorer outcome compared to multimodal treatment (HR 5.69, p=0.02), whereas the impact from one treatment modality was not significant (HR 1.52, p=0.49). Unadjusted and adjusted analyses are presented in table 3.

(Table 3 approximately here)

All three long-term surviving patients were females aged under 70 years with good performance scores (KPS $\geq$ 90), and two of them had histologically confirmed IDH1 wildtype glioblastoma. These two had both a severe midline shift, although highly different tumor volumes, with T1 volume, T2/FLAIR volume, and T2/FLAIR:T1 ratio of 11 cm^3 vs 140 cm^3, 108 cm^3 vs 255 cm^3, and 9.8 vs 1.8, respectively.

Two patients (5.6%) had stable disease with no sign of recurrence during follow-up. Thirteen patients (36.1%) had no period of improvement or stable disease after primary diagnosis, presenting with a continuous progression and deterioration until death, without being diagnosed with recurrence. In the remaining 21 patients (58.3%), an interval with improvement or stabilisation after primary treatment was observed, thereafter being diagnosed with recurrence. Nine of 21 patients (42.9%) diagnosed with recurrence received various anti-tumor treatments (table 2). Median post-recurrence survival was 7.7 months (95% CI 0.0-18.3) in patients receiving anti-tumor treatment, compared to 1.5 month (95% CI 1.3-1.7) in patients receiving best supportive care (p<0.01).

Discussion

In this retrospective population-based cohort study we found that 9.4% of adults diagnosed with glioblastoma met the criteria for butterfly glioblastoma. Outcome was poor, with a median overall survival of less than six months. This study adds real-world data on prognostic factors and outcome in a previously sparsely described subgroup of glioblastoma, whereas previous studies are based on data from tertiary referral centres [3-5, 8].

Survival

Our study confirms previous findings of a considerably poorer prognosis in butterfly glioblastoma compared to glioblastoma in general, where population-based studies observed a median overall survival of nine to 11 months [22-25]. A median overall survival of 5.9 months in our cohort was comparable to the results from previous butterfly glioblastoma studies, with median survival ranging from 3.2 to 5.9 months [4, 5, 8]. Survival was substantially poorer than that observed by Burks and colleagues, where median survival was 12 and 15 months in patients who underwent two different surgical approaches [6]. Likely explanations are different selection criteria and settings, and highly different resection rates of 16% and 100%. Although these two studies cannot be compared directly, this may indicate a potential benefit from a more aggressive treatment approach in patients with butterfly glioblastoma. Patients aged over 70 years received less intensive treatment than younger patients, and had a significantly poorer outcome with a median survival of only two months, equal to the findings of Dayani and colleagues [4]. Previous studies have demonstrated that combined chemoradiotherapy improves outcome in elderly glioblastoma patients with adequate performance status [26-28]. Future studies, preferably including quality of life analyses, may clarify if these results are applicable to the butterfly glioblastoma subgroup.

Despite the poor overall outcome, patients with long-term survival existed. Three- and five-year survival rates of 8.3% and 5.6% were comparable to the corresponding pooled survival rates of 11% and 4% in a large meta-analysis of glioblastoma in general [29]. We suggest that patients with butterfly glioblastoma might receive less-intensive treatment due to the deep-seated tumor location, uncertainty of treatment benefit, and the dismal prognosis. This study demonstrates that long-term survival is possible, supporting an argument for a higher treatment intensity in patients in acceptable general condition. A second argument for providing more multimodal treatment is the challenge in predicting treatment benefit, long-term survival, and quality of life in these patients. Only a minority of patients receiving TMZ suffered from significant toxicity, serving as a third argument to promote an increased treatment intensity in patients with butterfly glioblastoma.

Approximately 40% of the patients diagnosed with recurrent glioblastoma received anti-tumor treatment, and had a median post-recurrence survival of nearly eight months. We consider this unexpectedly long, and suggest that anti-tumor treatment may be appropriate in patients with recurrent butterfly glioblastoma and acceptable performance status.

MR volumetric analyses

Correlation analyses revealed a slight negative correlation between larger abnormal T2/FLAIR volumes and age, but without statistical significance. All four patients with the largest tumor volumes in T1-weighted MRI, and four of five patients with the largest abnormal T2/FLAIR volumes, were aged under 70 years. Among possible explanations, we suggest that younger patients, having a higher cognitive reserve, tolerate larger tumor growth before symptoms occur. In addition, IDH mutated glioblastoma is more frequent in younger patients, and is associated with less aggressive growth and larger tumor volumes, although this was not evaluable in this small sample [30].

Adjusted Cox regression revealed that larger abnormal T2/FLAIR volume was slightly negatively associated with survival. This negative prognostic value appears after adjustment for age and sex, most likely explained by higher age being a negative confounding variable. Younger age was strongly associated with longer survival, possibly masking the negative effect of larger T2/FLAIR abnormality in the unadjusted model. Nevertheless, the tumor volumes of long-term surviving patients differed widely, ranging from the upper to lower quartiles. We suggest that larger T2/FLAIR abnormality cannot be considered an unequivocal negative prognostic factor, as larger volumes may be seen in younger patients harbouring favourable prognostic factors. The association between T2/FLAIR volumes and age has not been studied previously, thus comparison with other studies was not applicable. Radiation therapy is a key modality in the treatment of patients with glioblastoma, but abnormal T2/FLAIR volume is not necessarily fully included in the Clinical Target Volume [31, 32]. Future studies should explore any associations between survival and the proportion of T2/FLAIR volume included in the target volume.

In our cohort, both median T1 and T2/FLAIR volumes were larger in the resection group than the non-resection group. Larger tumor volumes in younger patients and larger tumor volumes in frontal lobes, with favourable surgical accessibility, are possible explanations. In contrast, Dziurzynski and colleagues reported slightly larger, but statistically insignificant, median T1 volume in the non-resection group compared to the resection group, although ranges were wide in both groups and with no difference in FLAIR volumes [5]. Among possible explanations for these differences are the different settings, small sample sizes, low resection rates of 16% and 36%, and the lack of adjustment for molecular subgroups. Unlike Dayani and colleagues, who reported a slight negative correlation between larger T1 volume and survival, we found no such association [4]. Small sample sizes and wide range of tumor volumes may explain this uncertainty.

Strengths and limitations

Strengths of this study included the population-based study design and that all patients were followed up for seven years or until death. Furthermore, clinical information on all patients was available in a common electronic record, and T1-weighted and T2-weighted/FLAIR images were available in all patients. The small sample was the main limitation, related to the rarity of the condition, but is comparable to sample sizes in previous studies [3-5, 8]. Other limitations included the lack of histological samples in approximately 50% of the enrolled patients, causing a risk of inclusion bias, and the high

number of missing molecular data. Further, associations between treatment and outcome in elderly patients were inconclusive, as only a minority of elderly patients received multimodal treatment.

To conclude, outcome from butterfly glioblastoma was dismal, with a median overall survival of less than six months. However, long-term survival was comparable to that observed in glioblastoma in general, and multimodal treatment was associated with improved survival. This suggests that patients with butterfly glioblastoma may benefit from a more aggressive treatment approach despite the overall poor prognosis.

Declarations

Conflicts of Interest/Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Author contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Line Sagerup Bjorland, Kathinka Dæhli Kurz and Hege Sætran. MRI analyses were performed by Kathinka Dæhli Kurz. Hege Sætran was responsible for histopathological and molecular analyses. Statistical analyses were performed by Line Sagerup Bjorland and Anastasia Ushakova. All authors participated in the interpretation of the results. The first draft of the manuscript was written by Line Bjorland, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standard

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK Vest 2014/1931). Informed consent was obtained from patients alive at time of inclusion. Waiver of consent was approved for deceased patients.

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Tables

Table 1. Patient and tumor characteristics in 36 patients diagnosed with butterfly glioblastoma between 01/01/2007 and 31/12/2014		
	n	(%)
Patient characteristics		
Female	21	(58.3%)
Age ≥ 70 years	13	(36.1%)
Karnofsky Performance Status < 70	8	(22.2%)
Charlson comorbidity score ≥ 7	5	(13.9%)
Symptom(s) at time of diagnosis		
Cognitive impairment	23	(63.9%)
Headache	12	(33.3%)
Epilepsy	9	(25.0%)
Paresis	9	(25.0%)
Dizziness	7	(19.4%)
Central facial palsy	4	(11.1%)
Dysphasia	3	(8.3%)
Hemianopia	2	(5.6%)
MRI characteristics		
Main tumor location		
Frontal	11	(30.6%)
Temporal	9	(25.0%)
Occipital	8	(22.2%)
Deep-seated	6	(16.7%)
Parietal	2	(5.6%)
Corpus callosum affection [a]		
Rostrum/genu	24	(66.7%)
Body	27	(75.0%)
Splenium	14	(38.9%)
Tumor distribution		

Left skewed	14	(38.9%)
Right skewed	15	(41.7%)
Symmetric	7	(19.4%)
Tumor volumes		
T1-weighted contrast-enhanced MRI (cm^3)	40	(24-75)
T2-weighted/FLAIR MRI (cm^3)	159	(93-248)
Ratio T2/FLAIR:T1 volumes	3.3	(2.3-4.9)
Hypothalamus involvement	12	(33.3%)
Basal ganglia involvement	16	(44.4%)
Blood vessel affection	21	(58.3%)
Necrosis	29	(80.6%)
Flow void	23	(63.9%)
Mass effect [b]	19	(52.8%)
Histopathological and molecular characteristics (n=14)[c]		
Histopathological features		
Part of tumor with morphological features of low-grade glioma (WHO grade II)	2	(14.3%)
Part of tumor with morphological features of anaplastic glioma (WHO grade III)	1	(7.1%)
Glioblastoma (WHO grade IV) solely	11	(78.6%)
IDH1 mutational status		
IDH1 R132H mutation	3	(21.4%)
IDH1 R132H wild type	11	(78.6%)
MGMT promoter methylation status		
Inconclusive	2	(14.3%)
Methylated	4	(28.6%)
Unmethylated	8	(57.1%)
BRAF mutational status		
BRAF V600E mutation	0	(0.0%)
BRAF V600E wild type	14	(100.0%)
Tumor volumes and T2/FLAIR:T1 ratio presented as median (IQR), all others as absolute numbers		

(%). Tumor volumes defined as contrast enhancement and necrosis in T1-weighted MRI and tumor associated non-enhancing hyperintense lesions in T2-weighted/FLAIR MRI. [a]Sum exceeding 100% due to the affection of multiple regions in several patients. [b]Mass effect defined as midline shift ≥ 1 mm. [c]Presented as absolute numbers and % of patients with histological sample available for re-evaluation and molecular analyses. Abbreviations: MRI=Magnetic Resonance Imaging; FLAIR=fluid attenuated inversion recovery; cm^3=cubic centimetres; IDH1=Isocitrate dehydrogenase 1; MGMT=O(6)-methylguanine-DNA methyltransferanse.

Table 2. Treatment and complications in 36 patients diagnosed with butterfly glioblastoma between 01/01/2007 and 31/12/2014.		
	n	(%)
Primary treatment		
Surgery		
None	18	(50.0%)
Biopsy	12	(33.3%)
Resection	6	(16.7%)
Chemoradiotherapy		
None	6	(16.7%)
Short-course	20	(55.6%)
Stupp protocol[a]	10	(27.8%)
Number of adjuvant TMZ courses	3	(1-9)
Number of treatment modalities[b]		
None (best supportive care)	6	(16.7%)
1 modality	7	(19.4%)
2 modalities	17	(47.2%)
3 modalities	6	(16.7%)
Treatment at recurrence (n=21)[c]		
Best supportive care	12	(57.1%)
Surgical resection	2	(9.5%)
Stereotactic radiosurgery	1	(4.8%)
Re-irradiation	1	(4.8%)
TMZ monotherapy	6	(28.6%)
CCNU-based chemotherapy (PCV[d])	1	(4.8%)
Bevazicumab and nitrosoureas (CCNU or BCNU)	3	(14.3%)
Anti-tumor treatment last 30 days of life	7	(19.4%)
Complications during follow-up		
Surgical complications[e]	3	(15.8%)

Epileptic seizure	16	(44.4%)
Venous thromboembolism	10	(27.8%)
Hematotoxicity[f]	3	(13.6%)
Osteoporosis	10	(13.9%)

Number of TMZ courses presented as median (range), all others as absolute numbers (%). [a]Defined as the completion of radiation therapy (60 Gy in 2 Gy fractions) with concurrent TMZ and at least one of six planned TMZ monotherapy courses). [b]Surgical resection, radiation therapy and chemotherapy (TMZ). [c]Numbers include 21 patients where relapse was detected, while two patients with no sign of recurrence during follow-up and 13 patients who had a continuous deterioration and died without being diagnosed with recurrence were not included. [d]Procarbazine, Lomustine (CCNU), and Vincristine. [e]Complications among 18 patients who had undergone biopsy or resection included cerebral infarction and paresis (n=1), increasing and permanent paresis (n=1), and dysphasia (n=1). [f]CTCAE ≥ grade 3 among 25 patients receiving TMZ. Abbreviations: TMZ=Temozolomide; CCNU=cyclonexyl-chloroethyl-nitrosourea (Lomustine); BCNU=Bis (Chloroethyl) nitrosourea (Carmustine); CTCAE=Common Terminology Criteria for Adverse Events.

Table 3. Unadjusted and adjusted analyses on overall survival in 36 patients diagnosed with butterfly glioblastoma between 01/01/2007 and 31/12/2014.

Variable	Unadjusted		Adjusted for age and sex	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Male	Ref.		Ref.	
Female	0.87 (0.44-1.74)	0.70	0.77 (0.38-1.55)	0.46
Age (per year)	1.06 (1.03-1.09)	**<0.001**	1.06 (1.03-1.10)	**<0.001**
Tumor side				
Left	Ref.		Ref.	
Right	1.19 (0.56-2.55)	0.65	1.34 (0.61-2.96)	0.47
Equal	2.19 (0.85-5.64)	0.11	1.99 (0.74-5.31)	0.17
Main tumor location				
Frontal lobe	Ref.		Ref.	
Temporal lobe	2.45 (0.93-6.44)	0.07	1.73 (0.62-4.87)	0.30
Occipital lobe	1.77 (0.66-4.77)	0.26	1.71 (0.61-4.77)	0.31
Parietal lobe	0.41 (0.05-3.24)	0.40	0.84 (0.10-7.24)	0.87
Deep-seated	6.44 (1.97-21.06)	**<0.01**	5.24 (1.46-18.77)	**0.01**
MRI T1 volume (per cm^3)	1.00 (0.99-1.01)	0.98	1.01 (1.00-1.02)	0.15
MRI T2/FLAIR volume (per cm^3)	1.00 (1.00-1.00)	0.70	1.00 (1.00-1.01)	**0.04**
T2/FLAIR:T1 ratio (per unit)	0.99 (0.98-1.01)	0.32	1.00 (0.98-1.02)	0.79
Hypothalamus involvement	1.73 (0.84-3.54)	0.14	1.41 (0.67-2.97)	0.37
Basal ganglia involvement	1.52 (0.77-3.00)	0.23	1.66 (0.79-3.48)	0.18
Blood vessel involvement	0.73 (0.37-1.47)	0.38	1.17 (0.55-2.50)	0.68
Mass effect (per mm midline shift)	0.94 (0.86-1.02)	0.12	1.00 (0.92-1.10)	0.97
Necrosis	1.01 (0.43-2.34)	0.99	0.50 (0.20-1.25)	0.14
Flow void	0.84 (0.42-1.72)	0.64	0.99 (0.48-2.04)	0.97
IDH1 mutational status				
IDH1 R132H wild type	Ref.			

IDH1 R132H mutation	1.00 (0.26-3.79)	1.00	2.14 (0.38-12.02)	0.39
MGMT promoter methylation status				
Unmethylated	Ref.			
Methylated	0.56 (0.15-2.11)	0.39	0.31 (0.06-1.53)	0.15
Primary treatment				
Two or three modalities	Ref.		Ref.	
One modality	2.76 (1.11-6.89)	**0.03**	1.52 (0.46-5.06)	0.49
Best supportive care	9.45 (3.09-28.91)	**<0.0001**	5.69 (1.39-23.38)	**0.02**

HR, 95% CI and p values calculated by unadjusted and adjusted Cox proportional hazards regression. Deep-seated location defined as tumor mainly located in thalamus, basal ganglia, capsula interna, splenium corpus callosum, or mesencephalon. Tumor volumes in cubic centimetres (cm^3). Mass effect measured as midline shift in millimetres (mm). Volumes defined as contrast-enhancing tumor volume in T1-weighted MRI and tumor associated non-enhancing hyperintense lesion in T2-weighted/FLAIR MRI. Only patients with available histopathological samples were included in IDH1 and MGMT analyses (n=16). Treatment modalities included surgical resection, radiation therapy, and Temozolomide concurrent and/or adjuvant. P values <0.05 were considered statistically significant. HR=hazard ratio; CI=confidence interval; MRI=magnetic resonance imaging; FLAIR=fluid attenuated inversion recovery; IDH1=Isocitrate dehydrogenase 1; MGMT=O(6)-methylguanine-DNA methyltransferase.

Figures

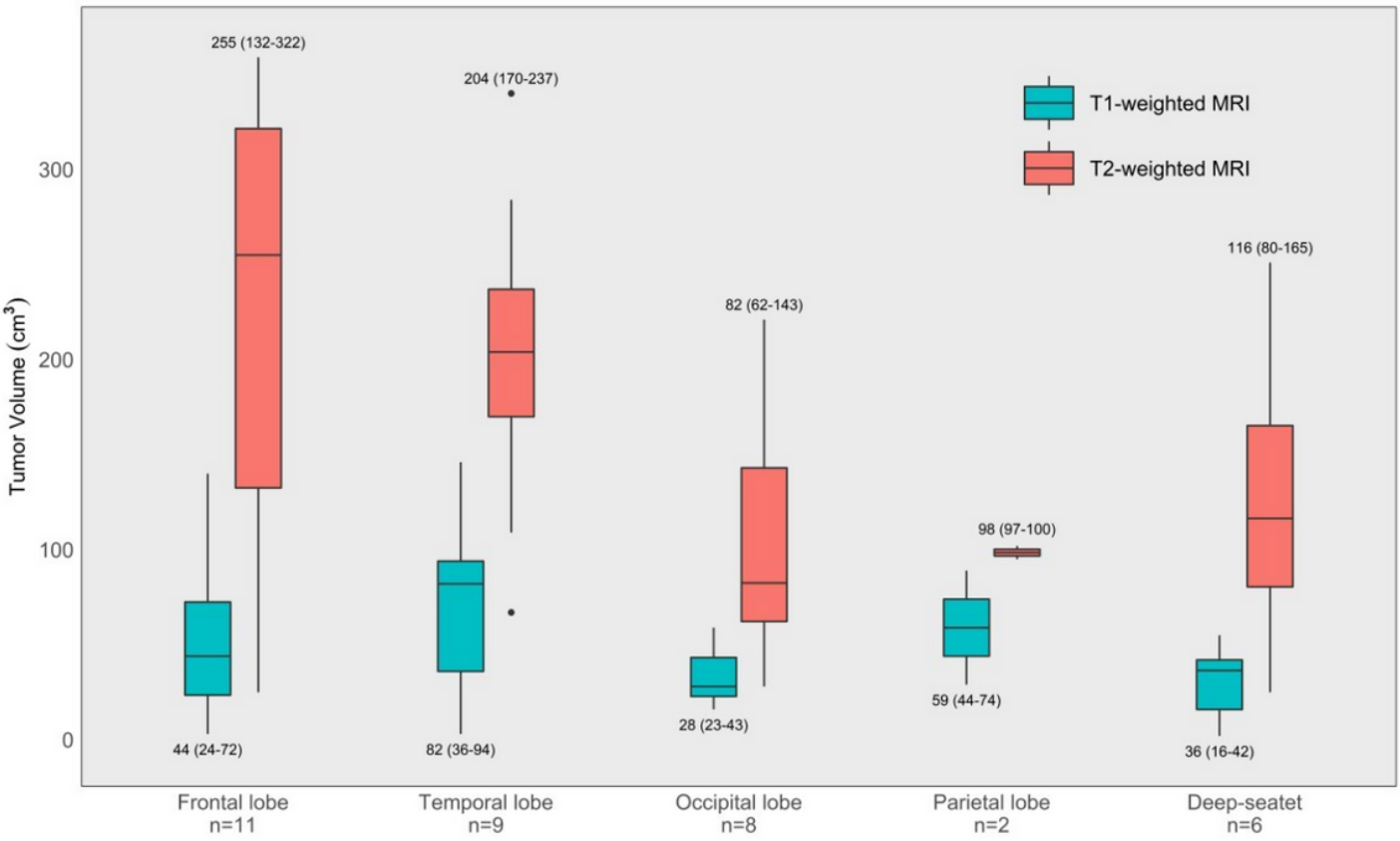

Figure 1

Median (Interquartile range (IQR)) contrast-enhancing tumor volume in T1-weighted Magnetic Resonance Imaging (MRI) and median (IQR) volume of tumor associated non-enhancing hyperintense lesions in T2-weighted and/or fluid attenuated inversion recovery (FLAIR) MRI according to tumor location in 36 patients diagnosed with butterfly glioblastoma between 01/01/2007 and 31/12/2014

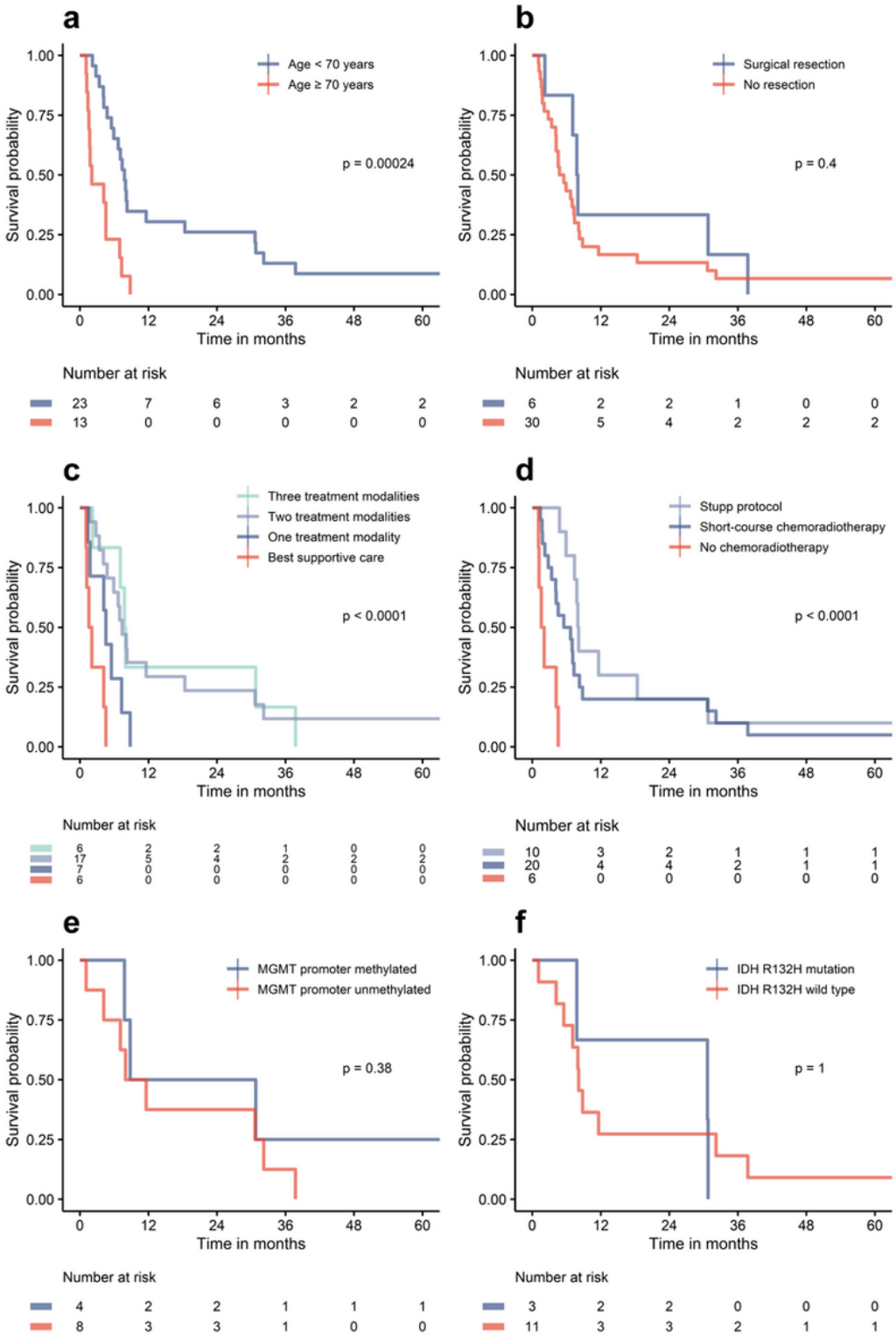

Figure 2

Kaplan-Meier curves of survival probability in 36 patients diagnosed with butterfly glioblastoma between 01/01/2007 and 31/12/2014. Cumulative survival in months. Survival by a) age, b) surgical resection, c) chemoradiotherapy regimen, d) number of treatment modalities, e) Isocitrate Dehydrogenase 1 (IDH1) R132H mutational status, and f) O(6)-methylguanine-DNA methyltransferase (MGMT) promoter

methylation status. Only patients with conclusive molecular analyses were included in curves e) and f). Comparison of groups by log rank test. P values <0.05 were considered statistical significant