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Butterfly glioblastomas: a retrospective review and qualitative assessment of outcomes

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Abstract

To address a paucity of literature and treatment guidelines regarding the management of butterfly glioblastomas, we performed a ten year retrospective analysis of data from twenty-three consecutive patients treated for this disease at a single institution. Clinical characteristics and outcomes were assessed. Median age was 59 years; 52 % were female; median preoperative Karnofsky performance score (KPS) was 80. Twelve patients underwent biopsy and eleven

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underwent surgical decompression. The median tumor volume for the biopsy group was 60.6 cm³ and for the surgically decompressed group 40.5 cm³. In the biopsy group, five patients received adjuvant therapy but one died prior to its completion; two died prior to the initiation of adjuvant therapy and five were lost to follow up. In the surgical decompression group, seven patients received adjuvant therapy, one died prior to the initiation of adjuvant therapy, two were treated with palliative measures only, and one was lost to follow up. Kaplan–Meier estimates of overall median post surgical-survival of the whole group was 180 days, the biopsy group 48 days, and the surgically decompressed group 265 days ($p = 0.14$). Our results show that there was a higher median survival in the surgically decompressed group; but a direct correlation could not be established, and that the median KPS did not improve in either group after treatment. A larger multi-center review is required to quantitatively assess the factors, including tumor biomarkers that are associated with patient outcome.

Keywords

Butterfly glioblastoma; Butterfly glioma; Bifrontal glioma; Bifrontal glioblastoma; Bihemispheric glioma; Corpus callosum glioblastoma

Introduction

Butterfly glioblastomas arguably represent the most aggressive form of glioblastoma multiforme. To date, objective assessment of a survival or clinical performance advantage in this patient population has not been performed. There is a paucity of objective data available to physicians that describe the clinical course and optimal management of this disease. Current management options include biopsy only, followed by radiation and chemotherapy; surgical decompression followed by radiation and chemotherapy; or biopsy followed by palliative measures (comfort care). Management decisions are subjective, based upon physician experience and/or patient/family preferences in light of the prognosis of this disease.

In this study, we retrospectively review the clinical and survival characteristics of this patient population at a single institution. Due to the rarity of this form of glioblastoma, the population number is small, despite our status as a tertiary referral cancer center. Thus our ability to apply multivariate analysis to identify clinical features independently associated with outcome was limited. Considering this limitation, we present our findings in a qualitative manner employing the use of descriptive statistics. This article will serve as the foundation for future investigations aimed at studying the best treatment paradigm for butterfly glioblastomas.

Methods

Patient population

Historically, the WHO has used the term “butterfly glioma” in reference to the spread and metastasis of glioblastomas. In their texts, they state: “A very common feature is extension of the tumour through the corpus callosum into the contralateral hemisphere, creating the

image of a bilateral symmetric lesion (butterfly glioma)” [1, 2]. We also performed a literature search in PubMed using the terms “butterfly glioma”, “butterfly glioblastoma”, “bifrontal glioma”, “bifrontal glioblastoma”, “bihemispheric glioma” and “corpus callosum glioblastoma” to find an established definition and criteria to classify a malignant glioma as a butterfly glioblastoma [3–13]. Such a definition or criteria was not identified. Our interest in this pathology was to study it as a subset of glioblastoma patients. Therefore, we use the term butterfly glioblastoma defined as the initial presentation of a grade IV astrocytoma with contiguous enhancement in bilateral cerebral hemispheres involving bilateral corona radiata by tumor crossing the corpus callosum (Fig. 1). To identify patients, we performed a retrospective review of the prospectively gathered M. D. Anderson Brain and Spine Center Multidisciplinary Database. This study was conducted with IRB approval. Search parameters included: an initial diagnosis of glioblastoma within the past 10 years from 2000 to 2010, bilateral disease location, and having undergone biopsy or surgical decompression. All records were retrieved and reviewed with verification of pathology and imaging characteristics. All tumors that could be classified as gliomatosis cerebri, multi-focal and/or multi-centric glioblastoma were excluded. Records of twenty-three individual patients were included in the analysis. Dates of death were verified through the MD Anderson Tumor Registry, whose staff obtains follow up on vital status for all patients seen at MD Anderson with a diagnosis of cancer, regardless of having definitive care at our institution.

Patient characteristics

All Karnofsky performance scores (KPS) utilized for the purposes of this study were recorded by either a neuro-oncologist or neurosurgeon, or estimated from the medical record based upon the dictated details of the patient’s functional status. Scores at the time of diagnosis, before, and after radiation therapy (XRT) are included. These scores represented the most consistent time points in which functional status was measured in the medical record. Tumor functional grade had been prospectively determined at presentation as described by Sawaya et al. [14]. Tumor volume had also been prospectively determined by volumetric analysis of individual patient MRIs using Vitrea 3.5 software (Vital Images, Inc., Minnetonka, MN). For the purpose of this paper and to provide a more accurate description of tumor mass, tumor volume was defined as the sum of T1 enhancement plus necrosis volume. Tumor flair volume data were also included. Extent of resection (EOR) represented the percentage reduction in T1 enhancing tumor volume on post-operative MRIs. Survival time was defined as the number of days from the time of diagnosis to date of death. Adjuvant therapy was defined as any treatment after the procedure (biopsy or decompression) and before progression, and consisted of XRT only, or radiation and chemotherapy.

We examined the distribution of tumor burden between cerebral hemispheres. At the time of initial data collection, T1 enhancement was measured and recorded exclusively as a single value determined from the measurements of the tumor as a whole. The determination of percentage of tumor burden per hemisphere and subsequent symmetry of bilateral involvement required re-tabulation using Vitrea 3.5 software. This was performed by volumetric analysis of T1 enhancement in each hemisphere, with separate measurements being made on the right and left sides of the midline. Tumors were defined as having a

symmetrical tumor burden if the difference in percentage of T1 enhancement between the right and left hemispheres was less than or equal to 10 %.

Statistical analysis

Descriptive statistics were performed and Kaplan–Meier plots were obtained. Log-rank was used to compare survival curves, and the Mann–Whitney *U* test was used to compare non-parametric data.

Results

During the study period, 792 patients with a new diagnosis of glioblastoma were seen at our institution. Of these patients, twenty-three patients (2.9 %) were identified that met our criteria of butterfly glioblastoma. All had undergone either surgical biopsy or decompression at our institution. Of these 23, six were lost to follow up. However, each patient except for one had sufficient documentation to indicate the planned course of treatment after their procedure.

Patient characteristics

Patient demographic data is summarized in Table 1. The median age at diagnosis was 59, with a range from 30 to 77. There were 12 females and 11 males. A total of 12 patients underwent biopsy and 11 underwent surgical decompression. In the biopsy group, adjuvant therapy was administered to five patients; two patients died before any adjuvant therapy could be initiated; and five patients were lost to follow up. In the surgically decompressed group, adjuvant therapy was administered to seven patients; two patients were palliated post-operatively, one patient died before adjuvant therapy could be initiated, and one was lost to follow up.

Clinical characteristics

Clinical characteristics are summarized in Table 2. The median KPS at diagnosis was 80, with a range from 30 to 100. Median tumor volume was slightly larger in the biopsy group, 60.6 cm³ compared to 40.5 cm³ ($p = 0.16$) in the decompression group. Flair volumes were equivalent. None of the tumors were confined to non-eloquent regions of brain; all were located either near eloquent or in eloquent areas. For patients who underwent surgical decompression, the median EOR of the enhancing tumor for either the adjuvant or palliation group was 100 %. Of the twenty-three patients, adjuvant therapy was planned post operatively (after either biopsy or decompression) for twenty. Of these twenty, only eleven completed an initial course of XRT. In the biopsy group, all five patients undergoing XRT received concurrent temozolomide. In the surgically decompressed group, three patients received XRT alone, three patients received radiation with concurrent temozolomide, and one patient underwent radiation with concurrent tamoxifen.

Outcomes

Median survival of our cohort of patients with butterfly glioblastomas was 180 days (95 % confidence interval, 0–380 days). Twelve patients were dead before 6 months (Kaplan–Meier estimate of survival at 6 months was 48 %) and only four survived longer than 1 year

(Kaplan–Meier estimate of survival at 1 year was 17 %). Three of these four patients had undergone surgical decompression—two with an EOR of 100 % and one with an EOR of 52.5 %. Median Kaplan–Meier estimate of survival for the patients having undergone biopsy was 48 days (95 % confidence interval, 0–111) and those having undergone surgical decompression was 265 days (95 % confidence interval, 91–439), although this result is not statistically significant, $p = 0.14$ (Fig. 2). Three patients in the decompression group died either just over or within 1 month. The remainder survived from 170 to 1,018 days.

Six of the eleven patients who underwent a decompression procedure had 100 % of the enhancing volume of tumor removed. Two of these six patients received palliative (comfort care) measures only and the remaining four survived from 265 to 1,018 days.

The patients with the two largest tumor volumes (greater than 100 cm³) both underwent surgical decompression. One presented with a KPS of 30 at diagnosis and survived just over 1 month. The other patient presented with a KPS of 90 and is still alive 431 days post procedure. EOR was 36.3 and 52.5 % respectively.

Formal cognitive evaluation was not performed for the majority of this patient cohort, so KPS was the best available measure of functional status. Of the total cohort of 23 patients, 16 presented with a KPS of 80 or greater at diagnosis. Of these 16, eleven survived at least 6 months. KPS at diagnosis was equal to or less than 70 for the remaining seven patients whose survival ranged from 15 to 331 days. Only one patient of these seven survived longer than 36 days. Among patients receiving adjuvant therapy following biopsy, KPS improved from the time of diagnosis to the conclusion of XRT in one and worsened in two. One stayed the same. Among patients receiving adjuvant therapy following surgical decompression, KPS improved in two, worsened in three, and remained the same in two.

Effect of symmetry of tumor burden on choice of procedure

We examined the distribution of tumor burden between cerebral hemispheres (Table 3) followed by an assessment of its influence on the type of procedure performed (Tables 3, 4). Tumors were defined as having a symmetrical tumor burden if the difference in percentage of T1 enhancement between the right and left hemispheres was less than or equal to 10 %. There were four patients with symmetrical tumors, all underwent biopsy. The median difference in symmetry was higher in the decompression group, however differences in percentages for this result were not statistically significant, $p > 0.1$. Although all patients who had undergone a decompressive procedure had an asymmetric tumor burden, the difference between this group and the biopsy group was not statistically significant, $p = 0.09$. Conclusions could not be drawn regarding a higher or lower likelihood of surgical decompression based upon the degree of symmetrical distribution of tumor burden.

None of the patients who had undergone gross total resection of their tumor (EOR = 100 %) had fully symmetric tumors. The range of difference in percentage of T1 enhancement between the two hemispheres was 16.2–100 %. Three of the five patients in this group had a difference in percentage of 34 % or less, indicating at least one-third of the tumor was located on the contralateral side.

Discussion

Researching the clinical features and optimal management strategies for patients with a butterfly glioblastoma, we were unable to identify a formal definition or any reports of case series or cohort studies describing the clinical course of these patients. The results of our literature search consisted primarily of isolated case reports, or reports of other pathologies that could mimic this disease process. The limitation of available literature on this presentation of glioblastoma underscores the need for such a cohort to be studied, and its clinical course reported. Since this a cohort is not currently available, we are unable to compare the results of our review to such a control.

Our results demonstrate heterogeneous outcomes. One factor is that different treatment regimens were used. Chemoradiation therapy was shown to provide a survival benefit for patients with newly diagnosed glioblastoma based on the publication by Stupp et al. in 2005 [15]. Hence, some patients in this study who were treated prior to 2005 received XRT alone. Four in the surgically decompressed group did not receive this regimen due to clinical factors such as anemia and poor functional status. During the transition to concurrent chemoradiation therapy, tamoxifen was prescribed as an alternative radiosensitizer for one patient.

Although we report longer median survival for the patients who had undergone surgical decompression, this result was not statistically significant. We cannot make any definitive conclusions that having undergone surgical decompression would improve survival compared to biopsy despite the observed trend. Since many patients in the biopsy group with shorter survival times were lost to follow up, closer examination of circumstances that could account for this outcome was not possible. This leaves two important questions unanswered. One, does a delay in the initiation of adjuvant therapy (principally XRT) contribute to shorter survival? Two, after having undergone biopsy only, does the remaining tumor's mass effect diminish a patient's ability to tolerate a full course of XRT? For the patients who did complete a full course of XRT, regardless of having undergone a biopsy or decompression procedure, median KPS at conclusion of this portion of adjuvant therapy was 70. The factors that contribute to the maintenance of a higher functional status could not be elicited from our small cohort.

It has been argued that aggressive surgical decompression should be undertaken in patients with butterfly glioblastoma to enable them to complete a course of XRT, either concurrently or with adjuvant chemotherapy. It is unknown if this paradigm would always represent the most appropriate course of action. In our review, one patient died during the course of XRT. This patient had not undergone surgical decompression and shortly after initiation of XRT succumbed to inability to control seizure activity. Several questions arise: (1) How often do such events occur? (2) In addition to seizure control, what other factors contribute to these patients not being able to tolerate a full course of XRT? (3) Could an aggressive decompression have prevented such an outcome? How much of the tumor would need to be decompressed? If, as a result of functional status of the brain harboring tumor, only a partial decompression is possible, is this sufficient? (4) How well does aggressive surgical decompression preserve meaningful functional status? Is it in the best interest of the patient

to prolong survival if such an endeavor results in that patient being unable to care for him or herself?

In our patient cohort, median EOR was 100 % in those patients having undergone surgical decompression. In this subgroup of six patients, the two patients with the longest survival presented with a KPS of 90, and maintained this KPS at the conclusion of XRT. The two patients to have received palliative measures only (comfort care) had presented with a KPS of 70. The final two patients in this subgroup presented with a KPS of 80 and 40, and both had a KPS of 50 at the conclusion of XRT. They survived 265 and 331 days respectively. Further review of this subgroup reveals no obvious relation between tumor volume and outcome. Our results, although limited, suggest that a balanced consideration of functional status as well as tumor burden should influence how aggressively surgical decompression should proceed.

We were unable to establish a direct correlation between tumor volume and presenting KPS. However, our results do show a tendency towards longer survival for patients presenting with a KPS greater or equal to 80. It would be important to determine in which patients' poor functional status were due to mass effect versus tumor destruction of vital and eloquent areas of brain (such as the hypothalamus or basal nuclei). In the former scenario, aggressive decompression would be predicted to improve functional capacity but would likely be of little consequence in the latter. Such information would help guide surgical decision making by helping to determine which patients with low KPS would be most likely to benefit from an aggressive procedure.

In our patient population, the median tumor volume for the biopsy group was larger than for the surgically decompressed group, despite that the two patients with the largest tumor volumes were both decompressed. The difference in median volume is not statistically significant. However, there is a wide range of volumes for both groups; 35.0–123.2 cm³ in the biopsy group and 0.8–178.1 cm³ in the decompressed group. Tumor volume was less of a determinant whether a patient underwent a decompressive procedure, rather the degree of mass effect or effect on functional status and subsequent ability to tolerate and gain benefit from surgery were the main factors.

We assessed our data to determine if a selection bias toward surgical decompression existed for the patients who presented with asymmetrical tumor burden. These patients are believed to be associated with lower surgical decompression morbidity due to a decreased degree of involvement of both frontal lobes. We selected a cut-off difference in percentage of tumor burden as 10 % to best represent those tumors with equal volumes of T1 enhancement in each hemisphere. We did not identify a statistically significant difference between the biopsy and surgical decompression group for difference in percentage of symmetry or the number of symmetrical tumors within each group.

Median survival of patients undergoing the Stupp regimen, where 83 % of patients had undergone prior decompression surgery, was 14.6 months [15]. In this group, 92 % carried a diagnosis of glioblastoma (not further characterized) and 86 % had a WHO performance status of 1 (KPS was not utilized in this study). Eight of our patients received radiation

with concurrent temozolomide, although not all received the exact Stupp regimen. There was one death prior to completion of XRT. The median survival of this biopsy subgroup was 296 days, whereas the median survival of this surgically decompressed subgroup was 608 days. Our patients who did receive radiation with concurrent temozolomide showed a tendency to survive longer.

The principal limitation in conducting this study at a single institution is the small sample size. As such, it may not be representative of all butterfly glioblastoma cases, and it significantly limits the ability to perform multivariate analysis. The goal of this study was to provide qualitative assessment of existing data to serve as a framework for a larger retrospective series/or prospective analysis involving multiple institutions. To date, our study is the largest reported series of these patients. Future studies should address the following: What constitutes aggressive surgical decompression and when is it appropriate to perform? Are there unique complications associated with partial reduction of tumor burden, such as seizure control, that still present challenges to patient management even when mass effect is reduced? Are there specific areas of brain involvement associated with better or worse outcomes, such as the hypothalamus, splenium of the corpus callosum, or basal ganglia? How best should quality of life be measured?

These questions may be answered by a multicenter study with a larger number of patients. Ideally, a prospective cohort design would be used. Such a design could more readily provide answers to the above questions as well as allow more detailed evaluations including formal neuro-cognitive and functional testing. In addition, biomarker analysis should be performed. The heterogeneity of our results may not purely be a consequence of study size. It could be indicative of an unmeasured phenomenon that drives the outcome of this disease for these patients. The determination of IDH1, methylation, and mutation status of these tumors could reveal a more profound biological determinant of fate. Such measurements are objective, and could ultimately serve as the initial decision point to lead the remainder of treatment management for these patients.

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Fig. 1. Representative patient MRI **a** coronal and **b** axial views demonstrating a butterfly glioblastoma. There is contiguous involvement of both hemispheres, with disease crossing the genu of the corpus callosum

Fig. 2.

Kaplan–Meier plots of **a** overall survival of the entire cohort of patients with a butterfly glioblastoma and **b** the cohort of patients having undergone surgical biopsy compared to the cohort having undergone surgical decompression. All patients were included regardless of having received adjuvant therapy. Median survival for the biopsy group was 48 days compared to the surgically decompressed group of 265 days, $p = 0.14$ (log-rank)

Table 1

Patient demographics

Total number	23
Age	
Median	59
Range	30–77
Race	
African American	0
Asian	0
Caucasian	20
Hispanic	3
Sex	
Female	12
Male	11
Procedure performed and subsequent therapy	
Biopsy	12
Adjuvant (confirmed)	5
Palliation	0
Decompression	11
Adjuvant (confirmed)	7
Palliation	2

Table 2

Patient and tumor characteristics

Procedure performed (study ID)	KPS at diagnosis	Tumor volume (cm ³)*	T1 enhancement (cm ³)	FLAIR volume (cm ³)	Involved corpus callosum	Tumor functional grade	EOR	KPS start of XRT	KPS end of XRT	Adjuvant therapy	Length of survival (days)
Biopsy											
5	90	44.5	37.8	56.2	Body	2	N/A	80	60	XRT + chemo	180
6	80	54.4	43	73.3	Body	2	N/A	80	50	XRT + chemo	339
8	80	35.8	25	55.6	Genu	2	N/A	N/A	90	XRT + chemo	639
9	80	52.4	34.3	137.1	Genu	2	N/A	Death	Death	Death	4
10	80	75.1	12.2	134.7	Genu	3	N/A	80	Death	XRT + chemo	16
13	60	123.2	113.8	121	Body	2	N/A	Lost to F/U	Lost to F/U	Lost to F/U	15
14	80	65.8	58.5	N/A	Body	2	N/A	Lost to F/U	Lost to F/U	Lost to F/U	71
17	90	89.6	56.5	N/A	Genu	2	N/A	Lost to F/U	Lost to F/U	Lost to F/U	199
19	80	63.3	42.2	N/A	Genu/body	2	N/A	Lost to F/U	Lost to F/U	Lost to F/U	48
20	70	105.5	44	89.5	Genu	2	N/A	Death	Death	Death	21
21	60	57.9	55.1	N/A	Splenium	2	N/A	Lost to F/U	Lost to F/U	Lost to F/U	34
23	80	35	16.2	122	Splenium	2	N/A	80	80	XRT + chemo	296
Median	80	60.6	42.6	105.2		2		80	70		48
Range	60–90	35.0–123.2	12.2–113.8	55.6–137.1				80	50–90		0–111**
Decompression											
1	80	40.5	23.8	75.3	Genu	2	100	60	50	XRT	265
2	90	41.9	32.6	62.5	Genu	2	100	70	90	XRT	1,018
3	70	56.2	53.1	155.5	Body	2	100	Death	Death	Palliation [†]	16
4	100	67.3	59.5	115.2	Genu	2	24.7	100	50	XRT + chemo [‡]	170
7	90	0.8	0.8	106.8	Genu	2	100	70	90	XRT + chemo	608
11	90	178.1	132.3	205.3	Genu	3	52.5	80	70	XRT + chemo	431+
12	30	129	62.2	178.2	Genu	3	36.3	Death	Death	Death	36
15	40	12.7	11.2	126.9	Genu	2	100	60	50	XRT	331
16	90	24.3	18.3	88.3	Genu	2	61.9	Lost to F/U	Lost to F/U	Lost to F/U	206
18	70	33.8	30.6	44.3	Body	2	100	Death	Death	Palliation [†]	25

Procedure performed (study ID)	KPS at diagnosis	Tumor volume (cm ³)*	T1 enhancement (cm ³)	FLAIR volume (cm ³)	Involved corpus callosum	Tumor functional grade	EOR	KPS start of XRT	KPS end of XRT	Adjuvant therapy	Length of survival (days)
22	80	39.5	33.1	35.7	Splenium	2	59.4	90	90	XRT + chemo	332
Median	80	40.5 [×]	32.6	106.8		2	100	70	70		265
Range	30–100	0.8–178.1	0.8–132.3	35.7–205.3			24.7–100	60–100	50–90		91–439 ^{**}

* Sum of T1 enhancement and necrotic volume

[‡]Tamoxifen

[†]Comfort measures only

^{**}95 % confidence interval

[×]*p* = 0.16

Table 3

Symmetry of tumor burden

Procedure performed (study ID)	T1 enhancement right (cm ³)	T1 enhancement left (cm ³)	% Symmetry right	% Symmetry left	Difference % symmetry*	EOR
Biopsy						
5	15.7	14.4	52.1	47.9	4.3	N/A
6	10.7	17.1	38.5	61.5	23.1	N/A
8	9.9	14.2	41.1	58.9	17.8	N/A
9	22.2	10.9	67.2	32.8	34.3	N/A
10	38.1	11.9	76.2	23.8	52.4	N/A
13	39.5	9.7	80.2	19.8	60.4	N/A
14	12.6	8.7	59.1	40.9	18.2	N/A
17	11.1	9.4	54.2	45.8	8.5	N/A
19	19.8	18.6	51.5	48.5	3	N/A
20	44.9	13.7	76.6	23.4	53.1	N/A
21	28.4	23.7	54.5	45.5	9.1	N/A
23	9.9	7.6	56.3	43.7	12.7	N/A
Median	17.7	12.8	55.4	44.6	18	
Range	9.9–44.9	7.6–23.7	38.5–80.2	19.8–61.5	3.0–60.4	
Decompression						
1	20.2	10	66.9	33.1	33.8	100
2	15.7	11	58.8	41.2	17.5	100
3	22.9	31.8	41.9	58.1	16.2	100
4	24	13.2	64.5	35.5	29	24.7
7	0	0.4	0	100	100	100
11	46.4	77.4	37.5	62.5	25.1	52.5
12	42.6	25.6	62.4	37.6	24.8	36.3
15	6.7	3.9	63	37	26.1	100
16	5.8	13.6	29.9	70.1	40.1	61.9
18	5	21.2	19.2	80.8	61.6	100
22	25.4	10.8	70.1	29.9	40.1	59.4

Procedure performed (study ID)	T1 enhancement right (cm ³)	T1 enhancement left (cm ³)	% Symmetry right	% Symmetry left	Difference % symmetry [*]	EOR
Median	20.2	13.2	58.8	41.2	29	100
Range	0–46.4	0.4–77.4	0–70.1	29.9–100	16.2–100	24.7–100

^{*} $p > 0.1$

Table 4Cross tabulation of symmetry and procedure ($p = 0.09$)

Procedure	Patients with symmetric tumor burden (10 % difference)	Patients with asymmetric tumor burden (>10 % difference)
Biopsy	4	8
Resection	0	11