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CLINICAL STUDY

Resection versus biopsy in the treatment of multifocal glioblastoma: a weighted survival analysis

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Abstract

Object Diffuse tumor invasion in multifocal/multicentric GBM (mGBM) often foreshadows poor survival outcome. The correlation between extent of resection in gliomas and patient outcome is well described. The objective of this study was to assess the effect of gross total resection compared to biopsy for mGBM on patient overall survival and progression free survival.

Methods Thirty-four patients with mGBM received either biopsy or resection of their largest enhancing lesion from 2011 to 2019. Relevant demographic, peri-operative, and radiographic data were collected. Tumor burden and extent of resection was assessed through measurement of pre-operative and post-operative contrast-enhancing volume. An adjusted Kaplan–Meier survival analysis was conducted using inverse probability of treatment weighting (IPTW) to account for the covariates of age, number of lesions, satellite tumor volume, total pre-operative tumor volume, degree of spread, and location.

Results Thirty-four patients were identified with sixteen (47.1%) and eighteen (52.9%) patients receiving resection and biopsy respectively. Patients receiving resection exhibited greater median overall survival but not progression free survival compared to biopsy on IPTW analysis ($p=0.026$, $p=0.411$). Greater than or equal to 85% extent of resection was significantly associated with increased median overall survival ($p=0.016$).

Conclusion Overall, our study suggests that resection of the largest contrast-enhancing lesion may provide a survival benefit. Our volumetric analysis suggests that a greater degree of resection results in improved survival. Employing IPTW analysis, we sought to control for selection bias in our retrospective analysis. Thus, aggressive surgical treatment of mGBM may offer improved outcomes. Further clinical trials are needed.

Keywords Glioblastoma · Extent of resection · Multifocal · Outcomes · Brain tumor

Introduction

Glioblastoma (GBM) accounts for 14.7% of all brain tumors but has the highest incidence of all malignant tumors with a poor prognosis (5.6% 5-year survival rate) [1]. Currently, the standard care for newly diagnosed GBM is maximal safe surgical resection followed by concurrent radiotherapy and temozolomide chemotherapy [2]. Over the last two decades, increased extent of resection has been associated with improved survival for high-grade gliomas [2–7]. In addition, increased extent of resection has been found to improve the efficacy of adjuvant radiation and chemotherapy in several studies possibly by reducing the burden of disease, reducing hypoxic behavior of tumor cells, and facilitating permeability and longevity of chemotherapeutic drugs [8].

In GBM, multiple enhancing lesions can be characterized as multifocal or multicentric. Multifocal lesions are suspected to arise from microscopic invasion along white matter tracts with communication between enhancing lesions on FLAIR imaging, while multicentric are thought to arise independently and are not connected on FLAIR [9]. For multifocal/multicentric glioblastoma (mGBM), gross total resection is often not feasible due to the diffuse nature of the disease process; therefore, typically a biopsy is offered

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in lieu of surgical removal. As such, patients with multifocal GBM have a significantly worse progression-free survival (PFS) and overall survival (OS) than those with unifocal GBM (i.e. GBM with a solitary lesion) (OS 6 months vs. 11 months) [10]. With such a dismal prognosis, there has not been conclusive studies on the optimal treatment paradigm for multifocal GBM. Given the preponderance of data supporting increased extent of resection (EOR) for gliomas, we sought to investigate whether decreasing the contrast enhancing burden of multifocal GBM was associated with improved outcomes. Here we conducted an exploratory study to investigate whether surgical resection of the dominant contrast-enhancing lesion was associated with improved survival compared to biopsy-alone patients.

Materials and methods

Patient selection

After Institutional Review Board Approval, a retrospective chart review was conducted of patients diagnosed with multifocal GBM between November 2011, and April 2019. Every consecutive patient that underwent resection or biopsy for a mGBM was included in our study. Inclusion criteria were as follows: (1) male or female subjects 18 years or older undergoing resection or biopsy for GBM, (2) pre-operative imaging indicated multifocal/multicentric disease, (3) the GBM was newly diagnosed (no previous chemoradiation), (4) patients underwent biopsy (stereotactic needle or open biopsy) or resection and (5) subjects presented with a pre-operative Karnofsky performance score (KPS) greater than 70. Patients were excluded if: (1) the disease was unifocal or initially unifocal followed by a recurrent multifocal form or (2) treated with stereotactic radiosurgery or laser ablation. Both multifocal and multicentric glioblastoma were identified contrast-enhanced T1 and FLAIR MRI and defined as previously described [9]. Patients in the resection cohort underwent craniotomy for removal of the largest contrast-enhancing lesion. Multiple simultaneous craniotomies for mGBM were not performed.

Data collection

Demographic information was collected from patient chart review. Presence of multifocal disease was confirmed through the evaluation of T1-weighted images with gadolinium contrast (T1C+). The number of lesions as well as lesion location, cortical and subcortical structures involved, degree of spread were recorded after evaluation of T1C+ and T2 FLAIR sequences. Radiographic evidence of three types of tumors spread was assessed: (1) perilesional, (2) periventricular, and (3) pericallosal/contralateral spread—defined as the presence of contrast-enhancing lesion within 1 cm of another lesion, ventricle, and corpus callosum or into the contralateral hemisphere respectively [11] (Fig. 1). Finally, pre-operative and post-operative volume of contrast-enhancing lesion was measured to assess tumor burden. All volumetric measurements were performed using the ImageCast (GE Healthcare, Chicago, Illinois) radiographic information system. Lesion volume was calculated per patient using free-hand measurements of tumor surface area multiplied by slice thickness to calculate tumor volume per slice, and then summating slice volumes, taking gaps between slices into account. Both pre-operative and post-operative lesion volume was calculated, and percent resection was recorded as the difference in tumor volume divided by pre-operative volume. Progression was defined through the RANO criteria [12] as $\geq 25\%$ increase

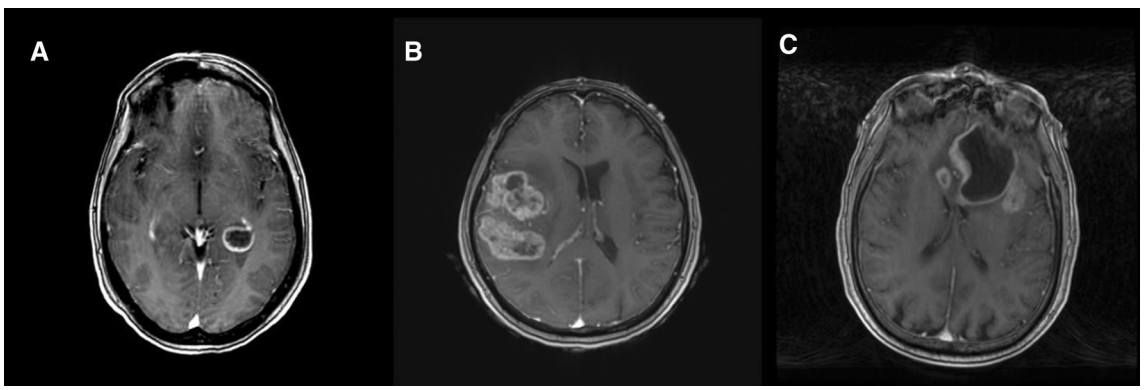

Fig. 1 **a**–**c** Representative contrast-enhanced FSPGR MRI radiographs representing three patients with mGBM and periventricular, perilesional, and contralateral spread respectively. **a** Patient with two left temporal lobe lesions (second lesion not shown) displaying isolated periventricular spread. **b** Patient with two large right, fronto-parietal lesions displaying peri-lesional and peri-ventricular spread to the posterior horn of the lateral ventricle. **c** Patient with a large, cystic left frontal tumor showing invasion of the corpus callosum, abutment of the anterior horn of the lateral ventricle, and two nearby smaller satellite lesions

in contrast-enhancing burden, presence of a new lesion (not present on initial MR), or symptomatic progression in the absence of steroid taper. Other information including completion of adjuvant chemo and radiotherapy, IDH1 mutations and MGMT hypermethylation status, and use of Avastin were also recorded.

Statistical analysis

All statistical analysis was performed using either IBM SPSS (IBM, Armonk, New York) or GraphPad Prism (GraphPad Software, San Diego, California). Kaplan–Meier (KM) curves were generated for OS and PFS and log-rank (Mantel-Cox) test and Pearson's Chi Square test was used to compare experiences between the resection and biopsy group. Patient's lost to follow-up were considered censored at the date of last follow-up in KM analysis. In order to account for confounding variables, we also analyzed OS and PFS using an inverse probability of treatment weighting (IPTW) KM and Cox proportional hazard model. The weighs used in IPTW are generated from the propensity scores, or the probability of being selected for the treatment (resection) versus control (biopsy) group in an observational study where physician bias is present, for each case.

The propensity score was generated using a logistic regression model with the following covariates: age at diagnosis, number of lesions, satellite tumor volume, spread (periventricular, contralateral, and perilesional), location (frontal, parietal, occipital, temporal, subcortical, cerebellum, and brainstem), and total preoperational tumor volume. Spread was specifically chosen as a covariate to account for easier access to enhancing volume in multifocal glioblastoma. The weight for each treatment group where then calculated as the inverse of the propensity score for the resection group and the inverse of one minus the propensity score for the biopsy group. Weights that exceeded a threshold value were truncated to prevent instability due to very large weights [13].

Cox Regression were run on the weighted sample to produce survival curves and hazard function curves that took into the account the following variates: treatment, age at surgery, extent of resection, and Avastin use (yes or no). MGMT hypermethylation and IDH1 mutational status were also included as covariates but in the context of a multiple imputation analysis to address missing data [14]. Ten imputations were conducted to simulate marker data for patients that did not undergo genomic testing.

Results

Patient demographics

A total of 34 patients were included in this study with an equal predominance between males and females (n = 34, M/F = 17, 50%). Eighteen patients underwent biopsy (52.9%) and 16 patients underwent resection of the largest contrast-enhancing lesion (47.1%). The most common approach used was a frontal craniotomy (47.1%), followed by temporal and parietal (23.5%, 20.6%). A summary of patient demographic data is detailed in Table 1. Pre-operative radiological data was assessed including volume of contrast-enhancing burden and the presence of three types of tumor spread (periventricular, perilesional, or contralateral).

Operative and treatment data

Periventricular, perilesional, and contralateral tumor spread was identified in 19 (55.9%), 18 (52.9%), and 16 (47.1%) patients respectively, as one patient can have multiple spread types. Pre-operative and post-operative tumor volume measurements were used to calculate the extent of resection for patients that received surgery. For the resection cohort, four patients (25%) received resection of greater than 85% of the contrast enhancing tumor burden; nine patients received less than 85% resection (56.3%); although follow-up imaging was present, immediate post-operative imaging was not available for three patients and thus extent of resection was unable to be calculated (18.7%). Twenty-nine patients completed standard of care adjuvant chemo- and radiotherapy (ChemoRT) after resection or biopsy (85.3%), three patients began but did not complete ChemoRT (8.8), and two patients were lost to follow up and thus treatment with ChemoRT was unable to be confirmed (5.9%). The mean pre-operative contrast enhancing volume was 64.3 ± 90.3 cm^3 ($\pm$ SD) and 59.4 ± 39.4 cm^3 for patients receiving resection and biopsy respectively. Pre-operative contrast enhancing burden was not significantly different between patients that underwent resection vs. biopsy ($p = 0.840$). Imaging, operative, and adjuvant treatment data are summarized in Table 2.

Mutational analysis

When available, data on IDH1 mutation and MGMT hypermethylation status was also recorded and compared between patients receiving biopsy and resection (Table 3). There was no significant difference in MGMT and IDH1 mutation status in patients receiving resection or biopsy ($X^2 = 3.147$, $p = 0.076$; $X^2 = 1.924$, $p = 0.165$).

Patient outcome

Only two cases of perioperative complications were observed. One patient experienced post-operative seizures and the other experienced altered mental status. Both complications occurred in patients that received

Table 1 Patient demographics and neurooncological data

Characteristic	Value (%)		
Patient demographic data	Total	Biopsy	Resection
Total patients (N)	34	18	16
Male	17 (50)	9 (50)	8 (50)
Female	17 (50)	9 (50)	8 (50)
Craniotomy side			
Right	18 (52.9)	8 (44.4)	10 (62.5)
Left	16 (47.1)	10 (55.6)	6 (37.5)
Craniotomy site			
Frontal	16 (47.1)	9 (50)	7 (43.6)
Temporal	8 (23.5)	4 (22.2)	4 (25)
Parietal	7 (20.6)	5 (27.8)	2 (12.5)
Frontotemporal	1 (2.9)	0	1 (6.3)
Temporoparietal	1 (2.9)	0	1 (6.3)
Occipital	1 (2.9)	0	1 (6.3)
Structures involved[a]			
Frontal	25 (73.5)	14 (77.8)	11 (68.8)
Parietal	13 (38.2)	8 (44.4)	5 (31.2)
Temporal	12 (35.3)	5 (27.8)	7 (43.8)
Subcortical	7 (20.6)	5 (27.8)	2 (12.5)
Occipital	6 (17.6)	2 (11.1)	4 (25)
Cerebellum	2 (5.9)	2 (11.1)	0 (0)
Brainstem	1 (2.9)	1 (5.5)	0 (0)
Neurooncological and treatment data			
Tumor spread[a]			
Periventricular	19 (55.9)	12 (66.7)	8 (50)
Perilesional	18 (52.9)	9 (50)	10 (62.5)
Contralateral	16 (47.1)	9 (50)	8 (50)
Extent of resection			
≥ 85%	4 (11.8)	0	4 (25)
< 85%	9 (26.5)	0	9 (56.3)
0% (biopsy)	18 (52.9)	18 (100)	0
No data	3 (8.8)	0	3 (18.7)
ChemoRT			
Completed	29 (85.3)	16 (88.9)	13 (81.3)
Incomplete	3 (8.8)	2 (11.1)	1 (6.2)
No data	2 (5.9)	0	2 (12.5)
Mean tumor size (± SD)	61 ± 68.35	59.43 ± 39.39	64.32 ± 90.25

[a]One or more types may be exhibited per patient (ex. A patient may have both periventricular and perilesional tumor spread)

biopsy and resolved by 6-month follow-up. Status at last follow up (stable, progression, or deceased) for patients receiving biopsy vs. resection is detailed in Table 3. Pearson's Chi-square analysis revealed a significant association between improved outcome—a lower proportion of progressing and deceased patients at last follow up—and resection ($p = 0.026$). Mean length to last follow up was 159.3 ± 130.8 days for patients receiving resection, and 217.1 ± 232.7 days for patients receiving biopsy and was not significantly different between groups ($p = 0.393$).

Survival analysis

KM curves were generated for patients receiving biopsy and resection and compared using log-rank (Mantel-Cox) tests. Patients receiving resection showed significantly higher median OS (16.6 months) compared to patients receiving biopsy (Fig. 2, 7.00 months; $p = 0.035$). Patients receiving resection also exhibited greater PFS (3.53 vs. 3.30 months) but this difference was not statically significant ($p = 0.484$). In addition, an IPTW analysis was

Table 2 Mutational markers

	Total biopsy	18
Biopsy	MGMT hypermethylation	
	No	9 (50)
	Yes	4 (22.2)
	No data	5 (27.8)
	IDH-1 (+)	
	No	12 (66.7)
	Yes	0 (0)
	No data	6 (33.3)
Resection	Total resection	16
	MGMT hypermethylation	
	No	5 (31.25)
	Yes	4 (43.75)
	No data	4 (25)
	IDH-1 (+)	
	No	10 (62.5)
	Yes	3 (18.75)
	No data	3 (18.75)

Table 3 Outcome data

Characteristic	Value (%)
Peri-operative complications	
Biopsy	2 (11.1)
Resection	0 (0)
Status at last follow-up	
Resection	
Stable	4 (25)
Progression	5 (31.3)
Deceased	7 (43.7)
Biopsy	
Stable	0 (0)
Progression	3 (16.7)
Deceased	15 (83.3)
Mean length to follow up	
Resection	159.25 ± 130.79
Biopsy	217.12 ± 232.743

conducted to control for physician bias that may have affected whether patients received biopsy or resection at presentation. The weighted KM curve showed the same median OS for resection group (16.6 months) compared to the biopsy group (7.0 months) as the unweighted KM curve but had greater statistical significance ($p = 0.026$). In the weighted model the comparison of PFS for the resected group (3.26 month) was almost equal to that of the biopsy group (3.30 months, $p = 0.411$).

Multivariate Cox Regressions were run to produce survival curves and hazard functions. The multivariate Cox Regression took into the account the following variates: age at surgery, extent of resection, and Avastin use. Both regressions were performed on the IPTW population. On multivariate Cox Regression analysis patients receiving biopsy did not have significantly shorter OS compared to resection (Fig. 3a, $p = 0.075$, HR = 1.38, 95% CI 0.870–18.05). However, the risk of progression for patients undergoing biopsy was significantly higher (Fig. 3b, $p = 0.009$, HR = 2.36, 95% CI 1.78–63.4). Additional Cox regression analysis was performed using all previous covariates with the inclusion of IDH1 mutation and MGMT hypermethylation status as variables. A multiple imputation approach with ten imputations was run to simulate the molecular status of patients that lacked marker data. Again, there was no significant difference in OS for biopsy compared to resection ($p = 0.161$, HR = 1.5, 95% CI 0.544–37.09), yet there was significantly higher risk for progression in the biopsy group as well ($p = 0.012$, HR = 2.33, 95% CI 0.1.67–63.34).

ROC analysis

ROC curves were generated to determine the optimum EOR threshold for predicting survival. Optimum EOR threshold was identified to be 85% EOR yielding sensitivity and specificity of 85.7% and 22.2% respectively. Area under the ROC curve (AUC) was 0.704 ($p = 0.081$, 95% CI 0.502–0.905). Similar analysis was performed for tumor progression, yielding sensitivity and specificity of 81% and 0% respectively with an AUC of 0.471 ($p = 0.803$, 95% CI 0.253–0.689).

Extent of resection analysis

Additionally, we evaluated the effect of extent of resection (EOR) on OS and PFS in patients at varying EOR threshold. EOR ≥ 85% compared to EOR < 85% yielded significant results. On IPTW KM analysis, OS was significantly higher in patients receiving greater EOR (Fig. 4a, 22.4 vs 8.4 months, $p = 0.015$). Median PFS was not significantly different between EOR ≥ 85% and < 85% (5.1 vs 5.6 months, $p = 0.576$, Fig. 4b).

Discussion

Here, we present, to our knowledge, the first retrospective, matched survival analysis of patients with newly diagnosed mGBM that received resection versus biopsy. Patients receiving resection showed significantly improved OS compared to patient receiving biopsy and a trend towards increased PFS, though not significant. After a

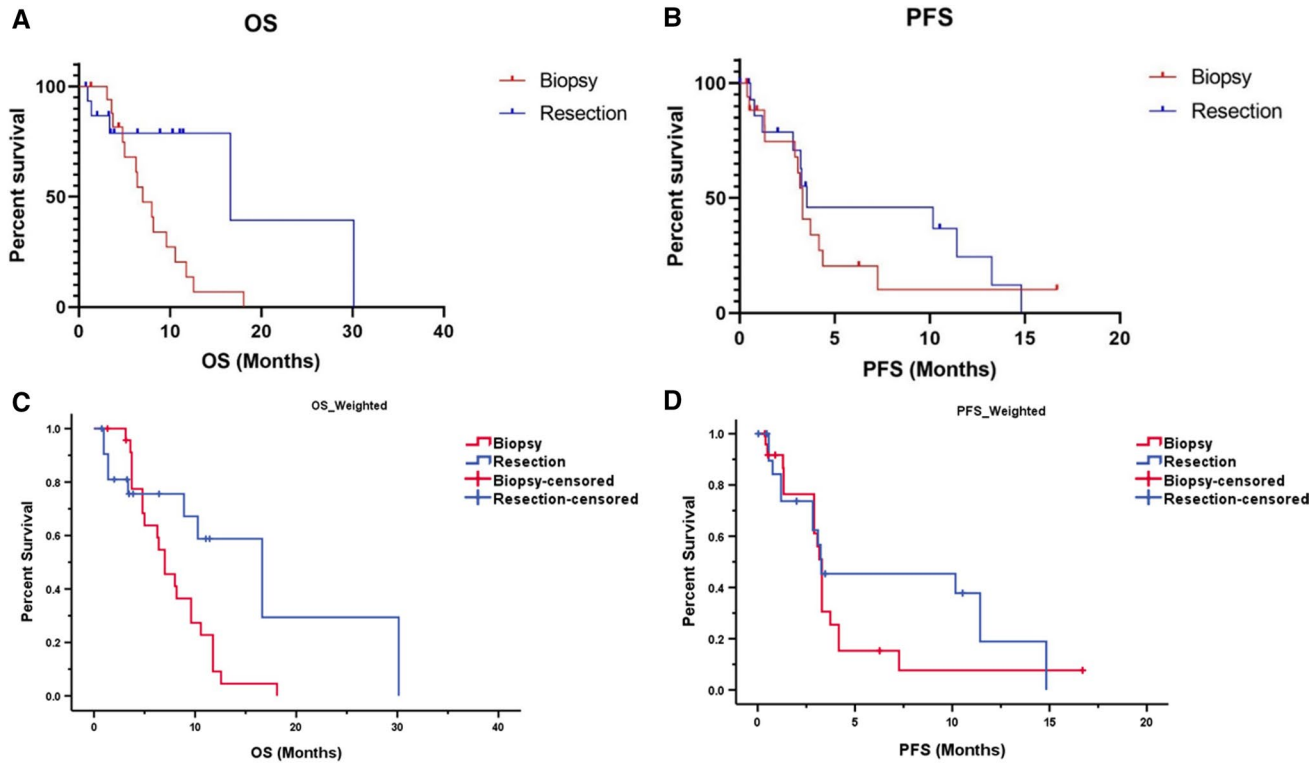

Fig. 2 **a**–**d** Unweighted and Weighted KM curves comparing OS and PFS in patients receiving resection (blue) vs. biopsy (red). **a** There was significantly greater median OS in patients receiving resection compared to biopsy ($X^2 = 4.433$, $p = 0.0353$). **b** PFS was not significantly different between groups ($X^2 = 0.4896$, $p = 0.4841$). **c** KM curve weighted using IPTW maintained a significantly greater median OS in patients receiving resection vs. biopsy ($X^2 = 4.956$, $p = 0.026$). **d** There remained no significant difference in PFS between the two groups ($X^2 = 0.677$, $p = 0.411$)

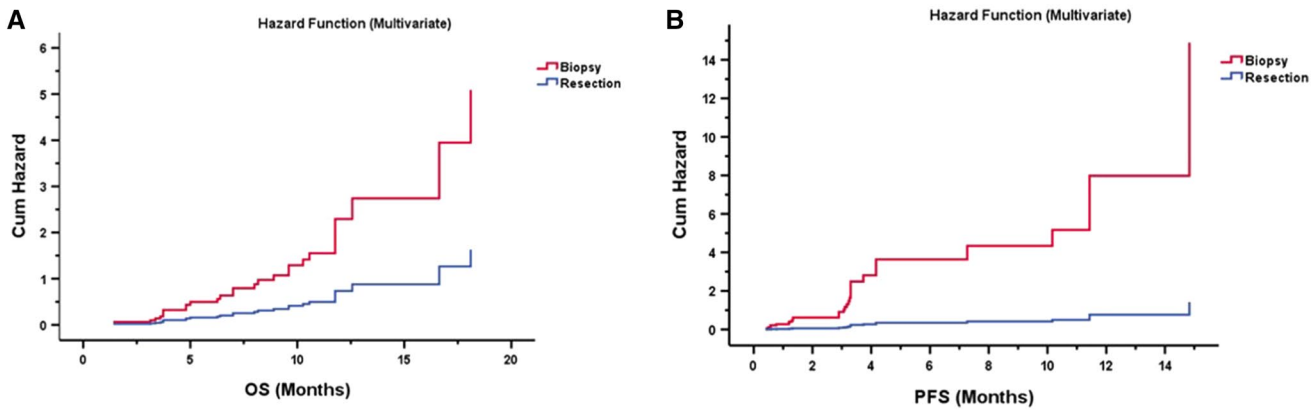

Fig. 3 **a**, **b** Hazard Function curves comparing OS and PFS in patients receiving resection (blue) vs biopsy (red). IPTW was generated for each patient. Multivariate Cox Regression was performed for treatment groups and adjusted for the following variates: age at surgery, extent of resection, Avastin use. **a** Multivariate Cox Regression model showed increased hazard of death for the biopsy group that was not significant ($p = 0.075$, $HR = 1.38$, 95% CI 0.870–18.05). **d** There was a significantly higher risk of progression with biopsy compared to resection ($p = 0.009$, $HR = 2.36$, 95% CI 1.78–63.4)

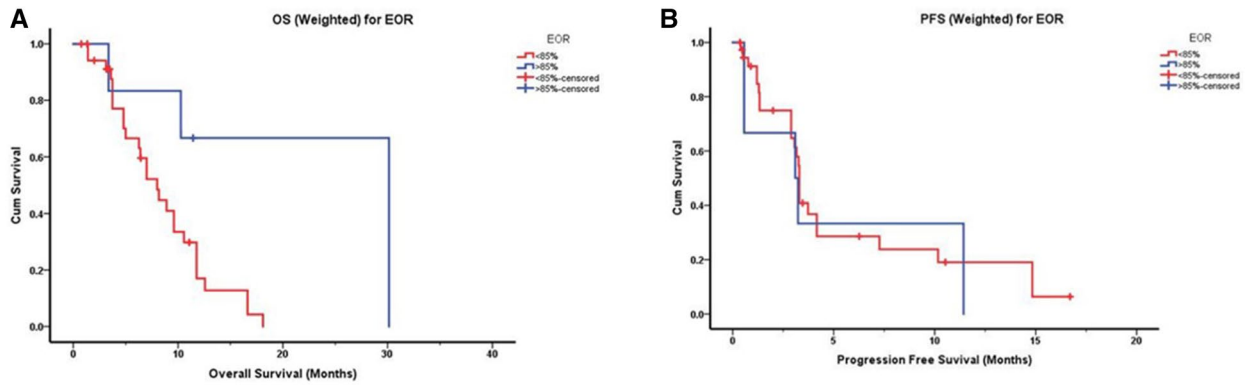

Fig. 4 **a**, **b** Weighted KM curves for patients with EOR ≥ 85% (red) vs. < 85% (blue). **a** IPTW analysis revealed a significant association between EOR and OS with 8.4 and 22.4 median OS for the EOR < 85% and EOR ≥ 85% groups respectively (p = 0.015). **b** Weighted KM curves for PFS showed patients with EOR ≥ 85% to have a median PFS of 5.1 months, not significantly different compared to median PFS of 5.6 for patients with EOR < 85% (p = 0.576)

propensity-matched analysis utilizing adjusted KM curves, a distinct trend towards increased OS and PFS was observed for patients receiving resection.

The proportion of mGBMs is substantial and ranges from 0.5% to 20% [10, 15–23]. The pathophysiological mechanisms underlying multifocality and multicentricity are not well understood and comprehensive molecular characterization of multifocal GBMs are just recently being reported [24]. Multifocal gliomas are believed to arise from microscopic spread from a single tumor while multicentric gliomas originate from individual foci [9]. It is believed multifocality may arise from the tendency of GBM cells to invade and migrate along white matter tracks and blood vessels [25–27]. Previous cytogenetic studies seem to support this theory implicating angiogenic gene aberrations such *EGFR* amplification, p53 mutations, and C-met expression in multifocal phenotypes [28–30]. As a result, mGBMs have a dramatically shorter median overall survival (3.3–5 months less than solitary disease) [10, 31].

Many consider multifocal and multicentric GBMs (mGBM) distinct radiologic entities. Multifocal GBMs are communicated through a larger area of T2-weighted signal abnormality while mGBM show no such connection. Aside from these definitions, however, multicentric and multifocal GBMs share many clinical and prognostic characteristics. Incidence of multifocal and mGBM is seen to be quite similar [32–34]. Multicentric and multifocal GBM also seem to share similar survival rates [9]. Indeed, Giannopoulos and Kyritsis have even gone so far as to say that "a strict definition between multicentric and multifocal gliomas has no practical clinical value" [35]. In either case, stereotactic biopsy seems to be the preferred approach to management. Thus, for this study, we included both multifocal and multicentric lesions in our definition of "mGBM". However, multicentric and multifocal lesions are still considered two distinct entities that are studied separately in many series. Therefore, there may be some value in investigating extent of resection and patient outcome between these two groups in future studies.

In the treatment of newly diagnosed GBM, there is clear evidence for improved outcome with an increased extent of resection [3–6]. Resection thresholds in which an improved OS and PFS was observed were originally established at 78% and 98% resection by Sanai [5] et al. and Lacroix et al. [3]. respectively. In 2014, a retrospective, multivariate analysis of 259 patients with nGBM suggested that a resection of 70% or more of contrast-enhancing tumor volume conferred significantly greater OS and PFS [36]. The differing thresholds in which increased extent of resection confers improved survival may be explained by the rise of novel adjuvant therapies, such as Temozolomide and Avastin, which may help reduce the burden of residual disease and potentiate radiotherapy [37]. We identified statistically significant improved median overall survival rates in patients undergoing resection compared to biopsy (16.63 vs. 7.00 months) when controlling for age, pre-operative tumor burden, mutational markers, and other pertinent covariates.

Through ROC analysis, we identified 85% EOR as the optimal resection threshold to achieve improved OS, though this was not significant (p = 0.081). However, it should be noted that ROC analysis is difficult with extended follow-up due to high rate of progression and low survivability in GBM and particularly mGBM. This may explain why EOR is a poor predictor of PFS as well as the low specificity due to low numbers of stable patients at later timepoints. Thus, survival analysis may be more accurate in measuring the effect of EOR on PFS and OS. We found patients that received resection ≥ 85% exhibited significantly improved median overall survival, closest to a threshold established by a previous report from Orringer et al. [38]. We hypothesize

that debulking may improve survival by alleviating mass effect, reducing intracranial pressure [39], instigating a local immune response [40], and cytoreduction [41, 42].

There is substantial evidence for a relationship between the degree of intracranial spread of GBM and prognosis. Parsa et al. compared post-progression survival (PPS) in 126 patients with single lesions with subependymal or subarachnoid spread (Type I, best prognosis), multifocal lesions without subependymal or subarachnoid spread (Type II, intermediate prognosis), and multifocal lesions with subependymal or subarachnoid spread (Type III, poor prognosis) [11]. A classic case of mGBM, butterfly glioma has a historically known poor prognosis; however, some series suggest that surgical debulking may confer an improved survival [43–46]. Nevertheless, in the management of patients with multifocal or mGBM, the degree of intracranial dissemination is often considered when assessing the benefits and risks of resection. Thus, in order to account for pre-operative selection bias, we included whether periventricular, perilesional, or contralateral spread was present in the generation of our propensity scores.

Age has been widely recognized as an important prognostic factor for patients with high-grade glioma [47]. Previous reports of have shown improved survival in younger patients (< 65) [10, 31, 48]. This relationship may be explained by increased incidence of co-morbidities, poorer performance status, lower rates of IDH mutations, and decreased ability to tolerate adjuvant therapies [47, 49, 50]. Additionally, there remains a discrepancy in the decision to pursue resection as patients increase in age [51]. Thus, we deemed it appropriate to include age as a covariate both in our generation of propensity scores and in our multivariate regression analyses.

While all of the patients included in our study underwent a single craniotomy for resection of a single tumor or two adjacent tumors, previous studies have detailed the use of multiple craniotomies for the resection of mGBMs and multiple brain metastases [16, 52]. Hassaneen et al. conducted a retrospective analysis of 20 patients with mGBM receiving multiple craniotomies in a single surgical session compared to 20 patients receiving a single craniotomy for unifocal GBM [16]. Patients were matched by pre-operative KPS score, tumor functional grade, extent of resection, age at surgery, and year at surgery. The authors achieved a median extent of resection of 100% in the mGBM group with nearly identical OS as patients with solitary lesions. The lack of increased complications associated with multiple craniotomies reported in this study suggests a potential role for aggressive surgery in the treatment of mGBM although larger studies are necessary to ensure these findings are reproduceable and generalizable.

Limitations

Our study has multiple limitations. It is limited by its retrospective, non-randomized design. Additionally, the ability to detect significant differences in outcomes may have been limited by the moderate sample size and insufficient statistical power. In addition, the patient population was heterogeneous with mean tumor volumes at presentation differing between patients receiving resection and biopsy, although these differences were not significant. The rates of IDH1 mutations and MGMT hypermethylation also slightly differed between groups, though this difference was not significant. Additionally, when mutational marker status was included as a covariate on Cox regression analysis, patients receiving resection continued to display reduced risk for progression and longer overall survival.

The role of selection bias in our retrospective series is worthy of discussion. The basis of selection between biopsy and resection is a potential source of confounding variables. It is likely that favorable tumor location, such as non-eloquent location, may have conferred improved survivability. Although there was no pre-specified algorithm used in deciding resection over biopsy, a key aspect in decision making was surgical accessibility of the largest enhancing nodule. Additionally, older patients with larger, invasive lesions may have been selected for biopsy due to concerns over the ability to tolerate a long surgery with extensive resection. Therefore, we attempted to account for these confounders through the generation for propensity scores using the covariates of age at diagnosis, number of lesions, satellite tumor volume, spread, location, and total preoperational tumor volume.

Indeed, future randomized trials evaluating the role of resection in the treatment of mGBM are warranted. However, the willingness of surgeons and patients to participate in randomization may prove a challenge. Due to the aggressive nature of the disease, not all patients with mGBM are able to tolerate extensive resection. Local tumor invasion may also compromise eloquent structures further calling in to question the viability of surgery. Future trials may seek to limit inclusion to only patients with surgically accessible lesions in non-eloquent cortex with adequate pre-operative functional status (e.g. KPS ≥ 70).

Conclusion

Treatment paradigms for mGBM remain controversial with the role of surgery yet to be clearly defined. Emerging evidence suggests EOR as a robust predictor of survival in patients with GBM. Our data suggests resection may confer increased OS in patients with mGBM compared

to biopsy. Additionally, improved survivability may be associated with increased EOR, concurrent with previous findings in unifocal disease. These data support a role for surgery in the management of mGBM and suggest a digression from traditional approaches of biopsy only. Future clinical trials evaluating the role of surgery in mGBM are desperately needed.

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Compliance with ethical standards

Conflict of interest The authors have no financial, personal, or professional conflicts of interest to disclose.

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