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Clinical trial participation of patients with glioblastoma at The University of Texas MD Anderson Cancer Center

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Abstract ***Background:*** It is estimated only 8–11% of patients with glioblastoma (GBM) enrol in clinical trials, limiting treatment development. We analysed the clinical and demographic features of patients with GBM enroled in clinical trials at the University of Texas MD Anderson Cancer Center (MDACC).
Methods: We reviewed the records of adult patients treated for primary GBM between 2007 and 2012 at the MDACC. A total of 755 patients were identified: 133 were deemed non-eligible, 111 were deemed trial eligible but received standard care and 511 participated in a clinical trial (311 for newly diagnosed glioblastoma [nGBM] and 200 for recurrent glioblastoma [rGBM]). Population characteristics were analysed using descriptive statistics, and survival end-points were evaluated with the Kaplan–Meier method.

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Results: The median age of clinical trial participants and trial eligible patients was 53.2 years (standard deviation 12.1). Most patients (49.4%) were enroled in a clinical trial protocol for nGBM. The majority of nGBM trial participants were male patients (65.1%), white (86.3%), married (84.4%) and in state (59.9%). Employment status, education, symptoms, tumour location, performance status, extent of resection and treatment facility differed between nGBM trial participants and non-participants. Patients who were eligible but did not enrol tended to be older, have worse performance status and live farther away from the MDACC.

Conclusion: Numerous disease and demographic barriers exist in trial enrolment in patients with GBM. This study highlights some of these obstacles, which require attention to improve patient enrolment to clinical trials. Patient and physician engagement in novel therapeutic strategies is essential to improving outcomes in this disease.

1. Importance of the study

Despite standard multimodal therapy, patients with glioblastoma (GBM) have a malignant trajectory, with an average life expectancy of less than 2 years from diagnosis. Novel therapies are essential to improve these outcomes, and patient participation in clinical trials is the necessary avenue to develop these treatments. However, only a minority of patients with GBM enrol in therapeutic clinical trials. Our retrospective study evaluates those demographic, social and disease-related factors associated with trial participation in patients deemed eligible for enrolment. Our findings identify multiple variables associated with trial enrolment, ranging from patient health behaviours to the nature of their neurologic symptoms. Clinical and academic attention to these factors may improve clinician counselling of patients around trial participation and introduce new elements to clinical trial design that will facilitate participation among patients with GBM.

2. Introduction

GBM is the most common malignant primary brain tumour in adults. It imparts a dismal prognosis, with a median overall survival (OS) of less than 2 years, despite standard multimodal therapies [1–3]. Barriers to therapeutic advancement include the low incidence of GBM compared with other cancers [4,5], its biologic complexity and the paucity of clinical trials available outside specialised centres. Clinical trials present a viable treatment option for patients with GBM, allowing potential improvement on standard therapy outcomes and contributing to our understanding of disease biology and therapeutic response. Furthermore, while patient and physician concern may arise that experimental therapies may jeopardise patient outcomes, there is evidence to the contrary, with trial participants having non-inferior, and even improved, survival outcomes in comparison with patients receiving standard of care treatment in other cancer types [6,7]. Despite this knowledge, it is estimated that only 3–9% of eligible cancer patients are treated in clinical trials and 8–11% of GBM patients, limiting progress in development of new therapies [8–11].

The precise factors that hinder clinical trial accrual in patients with GBM are poorly defined. In cancer patients, a breadth of factors may influence a patient's decision to participate, from the individual's relational autonomy to their larger social, political and economic context [12]. Patients with brain tumours warrant independent study in this regard, as they have a unique illness experience from other cancer patients. Owing to the nervous system involvement by tumour and/or side-effects from therapy, cognitive, behavioural and motor changes are commonplace, influencing the patient's decision-making, employment and functional independence. As such, they may have unique barriers to clinical trial enrolment. Further elucidating these barriers will be integral in improving access to experimental therapies for our patients.

The University of Texas MD Anderson Cancer Center (MDACC) is a large tertiary cancer care centre that provides clinical trial opportunities for patients with primary brain tumours, including GBM. This study evaluates patients with GBM eligible for clinical trial enrolment at our centre, comparing those who participated in clinical trial for newly diagnosed GBM with those who did not participate or participated in a trial at disease recurrence. This study was limited to patients with GBM as it is the most common malignant primary brain tumour in adults, the treatment approach at diagnosis is relatively homogeneous and most clinical trials in our department are designed for this disease entity. Studying this population provides an opportunity to evaluate both the influence of clinical trial enrolment on disease trajectory and compare the demographic and clinical profiles of those patients who enroled in clinical trials and those who were eligible but did not enrol.

3. Methods

3.1. Patients

In an institutional review board–approved retrospective study, we identified 755 adult patients (age ≥18 years) from our neuro-oncology database with primary GBM (no prior diagnosis of lower-grade glioma) diagnosed between 2007 and 2012 (Fig. 1). All cases were pathologically confirmed and had >1 visit at our institution. There were a total of 511 participants in clinical trials for GBM. Of these, 311 patients participated in a clinical trial that investigated the initial treatment of newly diagnosed glioblastoma (nGBM), with 76 of these patients also participating in one progressive or recurrent disease (recurrent glioblastoma, rGBM) trial and 16 participating in 2 rGBM trials subsequent to their nGBM trial participation. Two hundred patients participated only in a clinical trial evaluating therapy for rGBM. Two hundred and forty-four patients (N = 244) did not participate in clinical trials. A total of 133 patients identified were deemed ineligible for trial enrolment and will be analysed in a separate manuscript. The remaining patients (N = 111) were retrospectively deemed eligible for clinical trial enrolment but opted for standard of care treatment at the MDACC. This group of trial-eligible patients was identified by excluding those patients with any of the following: Karnofsky Performance Status (KPS) < 60 at diagnosis or after concurrent chemoradiation, prior bevacizumab exposure, early progression or death (before the start of adjuvant temozolomide) or another cancer active within 3 years.

3.2. Data analysis

Variables analysed included age, sex, ethnicity, social status, level of education, employment status, family oncologic history, medical comorbidities, KPS, presenting symptoms, tumour location, extent of resection, treatment modalities applied and level of specialisation of the centre where antitumour treatments were received. Survival endpoints included OS and progression-free survival (PFS). OS time was defined as the time from first surgery until death from any cause, and PFS, as the time from first surgery until objective first tumour progression or death, whichever occurred first. A patient was censored if he/she is alive without any event occurrence.

Data were summarised using standard descriptive statistics, including mean, standard deviation, median and range for continuous variables and frequency and proportion for categorical variables. Association between categorical variables was examined using the Chi-squared test or Fisher's exact test when appropriate. Wilcoxon rank-sum test or Kruskal–Wallis test was used to examine the difference on continuous variables between or among patients' characteristics groups. Univariate analyses were performed to select variables of interest for multivariate analysis. OS time and PFS time were estimated using the Kaplan–Meier method, and the comparison between or among patients' characteristics groups was evaluated using log-rank test. Both univariate and multivariate Cox regression models were applied to assess the effect of covariates of interest on OS and PFS. All computations were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC, USA), and R 3.2.4. P values < 0.05 were considered statistically significant.

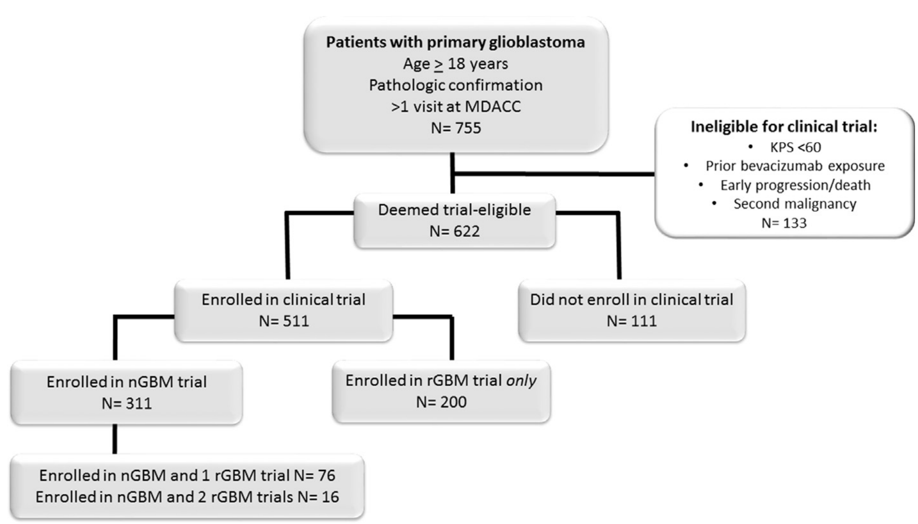

Fig. 1. Consort diagram of patients selected for the study. MDACC: MD Anderson Cancer Center, KPS: Karnofsky Performance Status, nGBM: newly diagnosed glioblastoma, rGBM: recurrent glioblastoma.

4. Results

4.1. General characteristics

The median age of all patients evaluated in this study (N = 622) was 53.2 years (standard deviation, SD 12.1), and on average, they lived 475.71 miles (SD 873.54) from Houston, Texas, where our centre is located. Demographic and clinical characteristics of patients are presented in Table 1 and Supplementary Table 1. Patients who participated in an nGBM trial lived significantly closer to our centre (mean 408.5 miles, SD 649.88) in comparison with those who did not participate (mean 542.94 miles, SD 1047.5, p = 0.042) when distance was analysed as a continuous variable. A larger proportion of patients who enroled in nGBM (N = 184, 59.9%) or rGBM (N = 122, 59.8%) trials were Texas residents, compared with those who did not enrol at any time (N = 52, 46.8%).

4.2. Variables associated with clinical trial participation

Education level (p = 0.046), functional status at diagnosis (p < 0.001), smoking history (p = 0.040), employment status (p = 0.006), presenting neurologic symptoms (p = 0.011), and extent of resection (p = 0.018) were significantly associated with participation in an nGBM clinical trial in comparison with those who participated in an rGBM trial or who did not enrol (Table 1). In comparing patients in an nGBM trial to those who never participated in a trial at any time, age (p = 0.0315), in-state residence (p = 0.021), presenting neurologic symptoms (p < 0.001), being a current smoker (p < 0.001), functional status at diagnosis (p = 0.002), tumour lateralisation (p = 0.046), surgical centre (p < 0.001) and radiation therapy centre (p < 0.001) were significantly different between groups.

The results of our univariate logistic regression analysis are given in Table 3. Patients with some college education (but without a degree) were 40% less likely to participate in an upfront trial, compared with those with at least a college degree (p = 0.002). Patients gainfully employed were 39% more likely to participate in a clinical trial than their unemployed, retired or homemaking counterparts (p = 0.003). There was a higher proportion of active smokers in the group who did not enrol in clinical trials (31.9%), in comparison with those who enroled in nGBM (5.2%) or rGBM (7.9%) trials (Supplementary Table 1). Patients with a history of smoking had a 28% (p = 0.049) lower chance of participating in an nGBM trial compared with patients who never smoked. The higher the quantity of cigarettes (packs/year) smoked, the less the chance of upfront trial enrolment (p = 0.024).

Patients who presented clinically with a KPS score from 60 to 80 (OR 0.35, p < 0.001) and of 90 (OR 0.60,

Table 1
Demographic and clinical characteristics of patient enroled in newly diagnosed GBM (nGBM) clinical trials vs those not enroled in nGBM trials.

Variable	Total	Enroled in nGBM trial		p-value
		Yes N (%)	No N (%)	
All patients	622 (100%)	311 (50.0%)	311 (50.0%)	–
Age (years)				0.269
<50	218 (35%)	117 (38.1%)	101 (32.1%)	
50-60	228 (36.7%)	109 (35.5%)	119 (37.8%)	
>60	176 (28.3%)	81 (26.4%)	95 (30.2%)	
Gender				0.084
Female	238 (38.3%)	107 (34.9%)	131 (41.6%)	
Male	384 (61.7%)	200 (65.1%)	184 (58.4%)	
Ethnicity				0.098
American Indian	3 (0.5%)	0 (0%)	3 (1%)	
Asian/Arabic	27 (4.3%)	17 (5.5%)	10 (3.2%)	
Black	21 (3.4%)	8 (2.6%)	13 (4.1%)	
Hispanic	43 (6.9%)	17 (5.5%)	26 (8.3%)	
White	527 (84.9%)	265 (86.3%)	262 (83.4%)	
Home state				0.0641
Texas	358 (57.6%)	188 (60.5%)	170 (54.7%)	
Other states	264 (39.9%)	119 (38.3%)	141 (41.5%)	
Other countries	16 (2.6%)	4 (1.3%)	12 (3.9%)	
Distance to Houston (miles)				0.371
<150	224 (36%)	116 (37.8%)	108 (34.3%)	
150–250	98 (15.8%)	53 (17.3%)	45 (14.3%)	
251–500	126 (20.3%)	53 (17.3%)	73 (23.2%)	
501–1000	112 (18%)	56 (18.2%)	56 (17.8%)	
>1000	62 (10%)	29 (9.4%)	33 (10.5%)	
Level of education				0.046*
10th grade	27 (4.7%)	11 (4%)	16 (5.5%)	
High school	113 (19.9%)	49 (17.6%)	64 (22%)	
Some college	139 (24.4%)	58 (20.9%)	81 (27.8%)	
Bachelor's degree	166 (29.2%)	90 (32.4%)	76 (26.1%)	
Advanced degree	124 (21.8%)	70 (25.2%)	54 (18.6%)	
Employment status				0.006*
Employed	245 (40%)	139 (46%)	106 (34.2%)	
Homemaker	51 (8.3%)	21 (7%)	30 (9.7%)	
Unemployed	219 (35.8%)	106 (35.1%)	113 (36.5%)	
Retired	97 (15.8%)	36 (11.9%)	61 (19.7%)	
Presenting symptoms				0.011*
Seizure	164 (26.4%)	93 (30.3%)	71 (22.5%)	
Focal neurologic symptoms	167 (26.8%)	82 (26.7%)	85 (27%)	
Headache	178 (28.6%)	87 (28.3%)	91 (28.9%)	
Dizziness	17 (2.7%)	10 (3.3%)	7 (2.2%)	
Altered mental status	82 (13.2%)	33 (10.7%)	49 (15.6%)	
Aphasia	10 (1.6%)	0 (0%)	10 (3.2%)	
Incidental	4 (0.6%)	2 (0.7%)	2 (0.6%)	
Tumour location				0.091
Frontal	217 (34.9%)	92 (30%)	125 (39.7%)	
Temporal	239 (38.4%)	130 (42.3%)	109 (34.6%)	
Parietal	110 (17.7%)	55 (17.9%)	55 (17.5%)	
Occipital	17 (2.7%)	11 (3.6%)	6 (1.9%)	
Thalamic/BG/PF	24 (3.9%)	10 (3.3%)	14 (4.4%)	
Multifocal	15 (2.4%)	9 (2.9%)	6 (1.9%)	
KPS at diagnosis				<0.001*
100	174 (28%)	108 (35.2%)	66 (21%)	
90	278 (44.7%)	136 (44.3%)	142 (45.1%)	
80	109 (17.5%)	39 (12.7%)	70 (22.2%)	
70	55 (8.8%)	21 (6.8%)	34 (10.8%)	
60	6 (1%)	3 (1%)	3 (1%)	

Table 1 (*continued*)

Variable	Total	Enroled in nGBM trial		p-value
		Yes N (%)	No N (%)	
Family history of cancer				0.014*
0	192 (30.9%)	92 (30%)	100 (31.7%)	
1-2	292 (46.9%)	160 (52.1%)	132 (41.9%)	
>2	138 (22.2%)	55 (17.9%)	83 (26.3%)	
Smoking history				<0.001*
Current smoker	47 (8.5%)	16 (5.2%)	31 (12.4%)	
Previous smoker only	183 (32.9%)	86 (28%)	97 (39%)	
Never smoker	326 (58.6%)	205 (66.8%)	121 (48.6%)	
Extent of surgical resection				0.018*
Biopsy	273 (45.3%)	156 (50.8%)	117 (39.7%)	
STR	34 (5.6%)	20 (6.5%)	14 (4.7%)	
NTR	194 (32.2%)	86 (28%)	108 (36.6%)	
GTR	101 (16.8%)	45 (14.7%)	56 (19%)	

*p < 0.050.
BG: basal ganglia, PF: posterior fossa, KPS- Karnofsky Performance Status, STR: subtotal resection, NTR: near-total resection, GTR: gross total resection.

Table 2
Upfront (newly diagnosed) clinical trials organised by therapeutic intervention and phase of trial.

Protocol type	Patients enroled
Therapeutic intervention	
Cytotoxic therapy	34 (11.1%)
Targeted therapy	134 (43.6%)
Immunotherapy/vaccine	2 (0.7%)
Differentiating agent	None in upfront setting
Device/other	None in upfront setting
Multiagent/combination therapy	137 (44.6%)
Phase of trial	
Phase I	77 (24.8%)
Phase II	173 (55.6%)
Phase III	57 (18.3%)
Unknown	4 (1.3%)

Analysed only for upfront clinical trial participants (n = 311).

p = 0.009) were significantly less likely to participate in an upfront trial compared with those with an intact functional status (KPS 100). While only 10 patients presented with aphasia, none of these were involved in upfront clinical trials. Eighty-two patients eligible for trials presented with altered mental status, but only 33 enroled in an upfront clinical trial. Patients who presented with seizure were 48% more likely to enrol in an upfront clinical trial than patients who presented with altered mentation (p = 0.017).

In regards to therapy, those patients who received biopsy or subtotal resection had 39% lower chance to participate in an upfront trial, compared with those with gross total or near total resection at presentation (p = 0.003). Patients who received radiation therapy at a community hospital or tertiary hospital had 77% (p < 0.001) and 62% (p < 0.001) lower chance of participating in an upfront trial, respectively, compared with those who were treated at the MDACC.

4.3. Survival outcomes: OS

The median duration follow-up time for the cohort was 8.7 years (95% confidence interval [CI]: 7.8–9.1) at the time of this analysis. Of the 622 patients evaluated, 559 (89.9%) had died. Median OS for the entire cohort is 1.9 years (95% CI: 1.7–2.0). The OS rate at 1 year (OS-1) is 84%, at 2 years (OS-2) is 45% and at 5 years (OS-5) is 16%. Patients who participated in an nGBM clinical trial had improved OS (p = 0.006, see Fig. 2A) when compared with those who did not participate (n = 111) or participated only at time of recurrence (n = 200). In a multivariate model controlled for gender, age, KPS and extent of resection, a persistent survival benefit was noted in patients who participated in an upfront clinical trial (hazard ratio = 0.54; CI: 0.43–0.67;

Table 3
Variables associated with participation in a clinical trial for newly-diagnosed glioblastoma.

Variable	Comparison	Odds ratio for trial participation	p-value
Age	<50 years vs > 60 years	1.32	0.169
	50–60 years vs > 60 years	1.05	0.828
Distance[a]	>250 miles vs ≤ 250 miles	0.73	0.106
Level of education	Less than college degree vs college degree or higher	0.58	0.001
Employment status	Unemployed/retired vs employed	0.59	0.001
Presenting neurologic symptom	Focal neurologic symptoms vs seizure	0.79	0.292
	Headache vs seizure	0.75	0.182
	Altered mentation vs seizure	0.52	0.017
	Aphasia vs seizure	0.04	0.030
KPS at diagnosis	60–80 vs 100	0.35	<0.001
	90 vs 100	0.60	0.009
History of smoking	Yes vs no	0.72	0.049
Extent of resection	STR or biopsy vs NTR or GTR	0.61	0.003
Location of radiation treatment	Community hospital vs MDACC	0.23	<0.001
	Other tertiary hospital vs MDACC	0.38	<0.001

STR: subtotal resection, NTR: near-total resection, GTR: gross-total resection, KPS: Karnofsky Performance Status, MDACC: MD Anderson Cancer Center.
[a] Distance from Houston, TX, location of the MDACC.

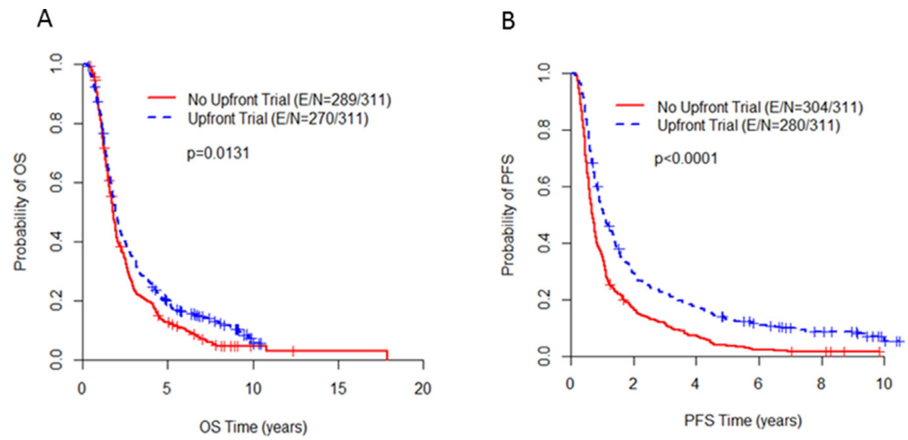

Fig. 2. Overall survival (A) and progression-free survival (B) of patients on upfront (newly diagnosed) GBM clinical trials and those not enroled on nGBM trials. OS: overall survival, PFS: progression-free survival.

$p < 0.001$). Trial type (Table 2) also had a significant influence on OS ($p = 0.010$), with those on a combination therapy trial having a 5-year OS of 27%, longer than those on an isolated cytotoxic agent (OS-5 = 15%) or targeted therapy (OS-5 = 14%). In comparison, the phase of nGBM trial (Table 2) did not influence OS ($p = 0.086$, see Supplementary Fig. 1).

Other variables with a significant impact on OS included age ($p < 0.001$), gender ($p = 0.005$), location of tumour ($p = 0.032$), KPS at diagnosis ($p < 0.001$), smoking history ($p = 0.016$) and radiation treatment centre ($p = 0.016$, Fig. 3A). While married people had a higher mortality rate ($p = 0.005$) and significantly shorter OS ($p = 0.029$) than others, marital status was significantly associated with older age ($p < 0.001$) and the sample size of unmarried patients was small, precluding a valid analysis. Male patients had a 35% higher mortality rate than female patients ($p = 0.005$), and each one-year increase in age of diagnosis was associated with a 3% higher risk of death ($p < 0.001$). Although ethnicity did not have a statistically significant impact on OS ($p = 0.187$), this may be owing to the paucity of non-white patients. Notably, the 21 African American patients in our study had longer OS in comparison with other groups, with OS-5 or 25% (in comparison to 16% for whites) and OS-1 of 95%.

More aggressive initial resection was associated with improved OS ($p < 0.001$); however, location of surgical centre of initial resection did not influence survival outcome ($p = 0.406$). When stratified by extent of resection, patients participating in an upfront trial had 19% lower risk of death, compared with those who did not participate in the upfront trial ($p = 0.016$).

4.4. Survival outcomes: PFS

At the time of analysis, 588 (94.5%) patients had disease progression or death. The investigator-assessed median PFS was 9.8 months (95% CI: 9.1–11.0). Participation in an nGBM clinical trial was associated with longer

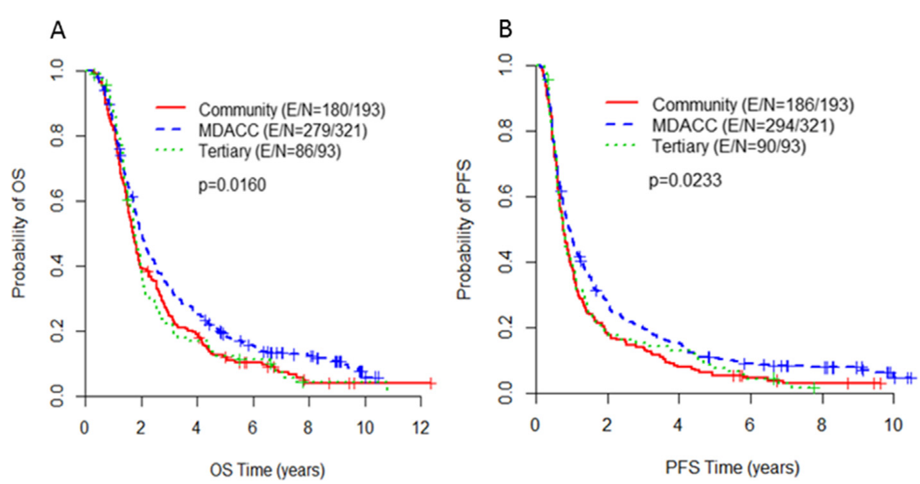

Fig. 3. Overall survival (A) and progression-free survival (B) of patients based on location of initial radiation therapy treatment: community hospital, other tertiary care centre and the MDACC. OS: overall survival, PFS: progression-free survival, MDACC: MD Anderson Cancer Center.

PFS ($p < 0.001$, Fig. 2B). Patient age ($p < 0.001$), presenting clinical symptom ($p = 0.003$), KPS at diagnosis ($p = 0.001$) and extent of resection ($p < 0.001$) had a significant impact on patient PFS. Enrolment on a protocol that used combination or multiagent treatment was associated with a longer PFS (PFS-2 = 34%, $p < 0.001$) compared with those enroled on trials of isolated cytotoxic (PFS-2 = 32%) or targeted therapy (PFS-2 = 23%), or those not enroled on trial (PFS-2 = 16%). Phase of nGBM trial also had a significant influence of PFS ($p < 0.001$), with patients on a phase I nGBM trial having shorter PFS (PFS-2 = 17%) than those on a Phase 2 (PFS-2 = 25%) or phase III (PFS-2 = 32%) trial. Although location of surgical centre of initial resection did not influence PFS ($p = 0.152$), the location of radiation treatment centre did have a significant influence ($p = 0.023$, Fig. 3B), with patients receiving treatment at the MDACC having improved PFS (PFS-2 = 27%), followed by those at other tertiary care centres (PFS-2 = 19%) and finally community hospitals (PFS-2 = 18%).

When stratified by extent of resection, patients who participated in an upfront trial had 37% lower rate of progression than those who did not participate in an upfront trial ($p < 0.001$). Male patients had 23% higher risk of progression compared with female patients ($p = 0.016$), and each one-year increase in age was associated with a 2% higher risk of progression ($p < 0.001$).

4.5. Survival outcomes: after first recurrence

Of the 534 patient who had at least one recurrence of their GBM, 504 (94.4%) had died at the time of analysis. The median survival for all patients after first recurrence was 9.96 months. When stratified by extent of initial surgical resection, OS from time of recurrence was influenced by participation in a clinical trial (upfront or at first recurrence), patient age and gender. Patients who participated in a trial at the first recurrence (with or without prior participation in an upfront trial) had lower risk of death compared with those who did not participate in trials at first recurrence ($p < 0.001$).

5. Discussion

Clinical trials present an important therapeutic option for patients with GBM and are vital in advancing patient outcomes in this field. Our study identifies distinct demographic, social and clinical profiles among clinical trial participants and trial-eligible patients with GBM. Our selection of trial-eligible patients as a comparator group allows for more focused analysis of those factors which influence patient decisions to participate in clinical trials. Knowledge of the factors that distinguish participant versus non-participant patients is imperative, as development of clinical trials that are representative of the breadth of GBM patients is integral to developing clinical research with strong external validity. Our outcome analysis emphasises the value of subspecialized care in GBM: enrolment in clinical trials and location of radiation therapy centre are interrelated treatment variables that are all associated with improved survival outcomes.

Education level was significantly associated with enrolment in clinical trials, with college-educated patients being 42% more likely to participate than others. Level of education has been shown to be a factor in patients' ability to quickly and comfortably make decisions about clinical trial participation in other studies [9,13–16]. This may not only be reflective of patients' health literacy but also of clinician skill in introducing clinical trials to patients in a manner appropriate for varied educational and vocational backgrounds. The quality of communication, a sense of alliance with the physician and presentation in language the patient understands have been found to be predictive of oncology trial participation [17], highlighting the importance of tailoring communication and education regarding trials to the individual patient. Patients with current employment were more likely to participate in clinical trials as well, which may reflect not only educational background but also economic stability, insurance status, social resources and functional capabilities, all potential factors in the decision to participate in clinical research, as well as physician recommendation of trial participation.

The demographics of clinical trial participants at the MDACC were similar to those reported in other large clinical studies [18,19]. While a statistically significant difference in trial participation between racial groups was not identified in the present study, disproportionately large numbers of white male patients enroling in trials has previously been reported [10,20–25]. Organised efforts, such as the Eliminating Disparities in Clinical Trials project [26], have been instituted to tackle these disparities and improve access to clinical trials, yet recruiting underrepresented populations for GBM clinical trials remains a substantial challenge [13,27]. These enrolment disparities are one fraction of the social inequities present throughout the US health care, of which economic burden, language barrier, lack of community partnerships, perception of medical research and cultural competence of physicians are all contributors [28–31]. While a significant difference in trial participation by gender was not noted in this study, male patients had poorer survival outcomes. This is consistent with the broader oncology literature, which has identified poorer survival outcomes in men [32,33]. Gender, however, has not been consistently identified as a prognostic factor in GBM [34], and its potential to influence on patient outcomes in this population warrants further exploration.

In-state residence was significantly more common in upfront trial participants than in patients who did not enrol in a trial, and an increased mean travel distance was noted in those who did not participate in clinical trials at any time point, suggesting this may be a barrier to trial enrolment. While travel distance did not have a significant impact on survival in our study, distance from the treating centre has previously been identified as a significant factor influencing quality of treatment and patient outcomes [35–37]. Travel can pose a barrier for many reasons: financial, social and logistical. However, incorporating novel care models and trial methodology could help mitigate this barrier. Use of novel telemedicine technology, which has helped expand the reach of tertiary care into the community in various aspects of medicine and is being expanded to include specialised oncology care [38], has the potential to reduce the effect of distance by reducing the number of visits needed [39]. Additional considerations to mitigate travel barriers could include collaboration with community centres to coordinate care or allowing universal and real-time reimbursement of expenses for travel and accommodation related to the clinical trial. The relationship between state of residence and insurance coverage is not clear; however, a potential relationship between these variables warrants attention in future study.

Smoking demonstrated a strong inverse relationship with upfront trial enrolment. Research in the breast cancer population has found that smokers are less likely to participate in clinical research [40]; however, the reason for this is unclear. A survey of cancer survivors found that smoking history was closely related to education level [41] and has also been associated with other patient-related and social factors including socioeconomic status, ethnicity, family status and employment status [42], which could all potentially predict enrolment in clinical trials as well. Finally, while not directly studied in cancer, poorer treatment compliance and a more erratic relationship with the health-care system have been identified in smokers [43], which may make a rigorous process with frequent clinical encounters such as a clinical trial less appealing within this population.

While the majority of clinical trials restrict enrolment to those patients with good functional status, our study found that, even among patients with adequate performance status (KPS $\geq$60), there was a significant association between better performance status and trial enrolment. Interestingly, we also identified presenting neurologic symptoms as being predictive of trial enrolment. Patients presenting with altered mental status have lower trial enrolment in comparison to those with other symptomatology, suggesting a cognitive symptom burden may be a barrier to clinical research participation. The precise reason for this is unclear. It may relate to the finding that patients with cognitive impairment or neurologic symptomatology may have reduced autonomy, which itself is closely linked to participation in clinical trials [44]. Providing informed consent for trial enrolment may also be limited in this population. The potential for physician bias, whereby trials are presented less frequently or effectively to patients with a cognitive symptom burden, is another possible barrier for participation. Notably, while only a small number of patients presented with aphasia ($n = 10$), none enroled in an nGBM clinical trial and only 1 in an rGBM trial. While this group is small, this suggests language dysfunction specifically may play a role in trial enrolment. Given the frequency with which cognitive impairment occurs in glioma [45], further exploration of this relationship is warranted.

Our data reveal significantly longer median survival in patients treated at the MDACC than those reported in large phase III GBM clinical trials [2,18]. The decision to move forward with a phase III clinical trial may be inappropriately influenced by comparison of outcomes from clinical trials performed at speciality centres such as the MDACC, highlighting the importance of using internal control populations, as recently described [46]. Notably, we found that the benefit of receiving radiation therapy at the MDACC persisted even when controlling for extent of surgery, age and performance status. Clinical trial enrolment, surgery at our centre and radiation therapy administered at our centre were significantly interrelated, and together, reflect receiving care at a subspeciality centre. At our centre, all patients with GBM are treated by clinicians with subspeciality expertise in nervous system cancers. While selection and referral bias to tertiary cancer centres such as the MDACC may contribute to this finding, the result is also reasonable to hypothesise that access to specialised care and access to novel therapies for these patients with GBM may have a positive role in their outcome. Subspeciality-trained neuro-oncologists are largely restricted to tertiary care centres, and given the relative rarity of primary brain tumours, general oncologists often have limited exposure to this tumour in comparison with other malignancies. Furthermore, the brain is a unique substrate for cancer, associated with distinct symptom burden and treatment toxicities. As such, the level of experience, comfort, expertise and treatment options for patients with GBM may be lesser at smaller centres.

Finally, these results reaffirm the improved survival outcomes of patients enroled in clinical trials. These improved outcomes were demonstrated in patients who participated in trials in both the upfront setting and at the time of recurrent disease, and this effect persists when analyses were controlled for variables such as age, gender and extent of resection. Variables that may contribute to improved outcomes in trial participants include patient selection and demographics, patient and physician expectations, treatment at a centre of expertise and more judicious clinical monitoring. The finding of improved outcome with trial participation in

GBM is valuable clinical information: participating in an experimental treatment may be anxiety inducing for patients and physicians alike; however, this finding supports clinical trials as a viable treatment option in GBM. Notably, a high proportion of patients who participated in an upfront clinical trial also opted to participate in another trial later in the disease course, affirming the perceived personal benefit patients have towards trial participation after initial participation [47].

This study does possess limitations. All patients evaluated in this study were treated at our centre, a tertiary cancer care centre, which may contribute to a distinct geographic, social, economic demographic in our patient population. As our database does not distinguish between GBM consults referred for newly diagnosed, recurrent or stable disease, our estimate of the proportion of patients who enroled on trial may lack accuracy. Despite their prognostic significance, molecular features such as isocitrate dehydrogenase (IDH) mutation status and O^6-methylguanine-DNA-methyltransferase (MGMT) methylation status are not available for the majority of these patients and thus not analysed in this manuscript. The retrospective nature of this study also limits the extent and breadth of data extracted for some patients, and as such, some clinical and survival data may be missing for certain patients. Trial eligibility was determined retrospectively, using common inclusion and exclusion criteria used in neuro-oncology trials. This method lacks the precision of prospective eligibility determination and does not allow for all the potential patient- and disease-related factors that can contribute to patient enrolment on trial. It is also important to acknowledge the role physician bias and pattern of practice may influence the presentation of clinical trial enrolment to an individual patient, variables which we feel would be valuable areas of future study. Despite these limitations, this study was performed on a large volume of clinical data and contributes valuable information to our understanding of clinical trial participation in patients with GBM.

6. Conclusions

This study highlights patient- and disease-related challenges in enroling GBM patients in clinical trials and confirms improved survival outcomes of GBM clinical trial participants as seen in other cancers. Innovative trial design and collaboration among academic and community centres to minimise the travel distance required for trial participation may improve enrolment. Clinician attention to the individual patient's symptom burden, education background and employment status may also help facilitate enrolment. Furthermore, academic investment in exploring those factors that influence trial enrolment in minority populations will be central to improve both trial enrolment and the generalisability of generated data. Improved survival outcomes have been found in patients who enrol in clinical trials and in those treated at a tertiary medical centre. This emphasises the importance of dedicated subspecialized care for patients with GBM, which can improve the outcome of this devastating disease. Ultimately, both clinician and patient investment in novel therapeutic approaches are essential to the innovation of GBM therapy.

Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.02.007.

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