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Clinical Study

Clinical trial participation and outcome for patients with glioblastoma: Multivariate analysis from a comprehensive dataset

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common malignant brain tumor in adults. Although multiple clinical and tumor-related variables affect survival outcomes, the effect of clinical trial participation has not been explored. The aim of this study was to determine whether clinical trial participation improves outcome for patients with GBM. Data from patients with GBM were accessed from a dataset collected over 12 years (1998–2010) at two institutions. Univariable and multivariate logistic regression analyses were performed to look for relationships between clinical trial participation, other baseline clinical and sociodemographic variables and overall survival (OS). In total, 542 patients were identified and included in the analysis; median age was 62 years. Sixty-one patients (11%) were enrolled in a clinical trial. Clinical trial enrollment was associated with improved median survival (14.5 months compared to 6.3 months, $p < 0.001$) and this difference remained significant in multivariate analysis (hazard ratio 0.67, $p = 0.046$). Age, poor performance status and operation type were also independent predictors for OS in multivariate analysis. Disease site, socioeconomic status and co-morbidity did not affect survival outcome. This is the first study in patients with GBM to suggest a survival benefit from clinical trial participation, independent of age and performance status; while also confirming the importance of other previously reported prognostic factors. This should encourage clinicians to offer trial therapies to patients with GBM and encourage patients to participate in available studies.

1. Introduction

Glioblastoma multiforme (GBM) is the most common and most aggressive malignant glial tumor, accounting for 60% to 70% of malignant gliomas. It carries a high mortality and a high social burden to both cancer sufferers and their carers. For patients treated on the landmark European Organisation for Research and Treatment of Cancer (EORTC) trial, the 2-year and 5-year overall survival (OS) rate was 27% and 9% respectively; with a median OS of 14.6 months.[1] Population studies suggest worse survival outcomes, with a median survival of 7 months and 5-year survival of only 3% in a large retrospective study of patients with GBM.[2]

It would be ideal to understand why there appears to be a spectrum of survival outcomes ranging from months to years to be able to identify prognostic factors at the outset of a patient's diagnosis, to detect inferior treatment strategies that could be modified, and to individualise management strategies. With more treatment options available, identifying those who may be most (or least) likely to benefit from a treatment becomes of paramount importance.

Clinical trials are the benchmark by which new treatments become established. Despite their importance, only a small percentage of patients with cancer are enrolled in clinical trials.[3] Participation in trials, for many with cancer, appears to improve outcomes regardless of the treatment arm allocated.[4] Surprisingly, whether this is true for patients with GBM has never been investigated to our knowledge. This is particularly pertinent as treatment options and clinical trials for patients with GBM have expanded in recent years, reflecting recent developments in targeted therapies and the increasing understanding of biological mechanisms behind malignant disease processes.

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The aim of this project was to correlate clinical trial participation and other sociodemographic and clinical variables with outcomes in patients with GBM, to identify potentially significant and possibly novel factors associated with survival outcomes in this disease.

2. Methods

2.1. Patients

This retrospective cohort study included all consecutive patients with GBM (World Health Organization [WHO] grade IV astrocytoma) diagnosed over a 12-year period (1998–2010) at two co-located hospitals (one public, one private), in Victoria, Australia. Both hospitals are neurosurgical and neuro-oncology tertiary referral centres. Given that the same clinicians work in both hospitals, patients are managed with consistent strategies and management protocols between the two hospitals.

2.2. Dataset

The Australian Comprehensive Cancer Outcomes Research Database (ACCORD) dataset for neuro-oncology was designed and developed by a panel of experienced neurosurgeons and neuro-oncologists. The dataset includes comprehensive clinical information from diagnosis, demographics and co-morbidities, to surgery and post-operative treatment, through to progression and ultimately death. Data, where available, from every patient diagnosed with a GBM (or other brain tumor) are entered prospectively. An updated and significantly more comprehensive version of the database was developed in 2007, resulting in some missing data for some variables of interest, in particular for patients diagnosed prior to 2007, due to the limited nature of the dataset prior to this time. The missing data were added to the database where available from chart reviews, but this was not possible in all cases.

Data were linked and analysed using BioGrid Australia, a novel concept in Australian and international biomedical research that has successfully implemented prospective and standardized data capture, and that links data from multiple disease and research databases within and between hospitals in a uniform, de-identified manner.[5] Collection of data at the hospital is privacy-protected and Human Research Ethics Committee-approved; and this project was also approved by the BioGrid Scientific Advisory Committee.

2.3. Clinical trial participation

A hospital cancer clinical trial database was used to verify that patients listed on the ACCORD database as participating in a clinical trial were enrolled in a trial. This was also used to determine whether the trial was a first line trial (defined as a chemotherapy and/or targeted therapy trial as part of the post-surgical management, prior to first recurrence), as participation in a second-line or third-line trial could create survivorship bias. As such, clinical trial participation was analysed in two ways: (i) any clinical trial, and (ii) first line clinical trial participation.

2.4. Sociodemographic and clinical variables

In addition to clinical trial participation, variables known from prior research to affect outcomes in patients with GBM, and also potentially novel factors that have not been researched significantly regarding their impact on GBM-related outcomes, were analysed using both univariate and multivariate analysis.

The selected sociodemographic variables included: age; gender; Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) score[6]; country of birth (Australia compared to other countries); whether an interpreter was required for hospital appointments; residence (major city compared to a regional centre); and a public compared to a private hospital.

Socioeconomic status (SES) was measured by the IRSAD score utilizing 21 variables, which included the proportion of high income households, low income households, and the proportion of people aged 15 years or over attending a university or other tertiary institution, in a particular area to assign a score dependant on these variables.[6] The scores were then standardised and arranged into deciles; higher deciles indicating relative advantage and lower deciles indicating relative disadvantage.

Clinical variables included the Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis; diabetes and smoking history; location of the tumor (frontal, lobar, deep or other); tumor size (measured on preoperative imaging); presence of multifocal disease; type of operation (biopsy or craniotomy); extent of resection (biopsy, partial resection [<50%], subtotal resection [50–95%] or gross macroscopic resection, as determined by postoperative imaging); and number of operations performed.

2.5. Survival

The date of death was obtained through linkage with the Victorian Cancer Registry (VCR), where all deaths in Victoria are mandatorily recorded. If death date was not recorded for a patient at the VCR, the date of last follow-up or last pathology or radiology investigation at the hospital (whichever was later) was used as the date at which patients were last known to be alive and patients were censored at this date for survival analysis.

2.6. Statistics

Both univariate and multivariate Cox logistic regression analyses were used to look for associations between OS and sociodemographic and clinicopathologic variables. For the univariate analysis, the log-rank test was used to test for associations between survival and categorical variables, while Cox regression was utilised for continuous variables such as age. Kaplan–Meier curves were estimated to illustrate the association and non-associations between survival and the categorical variables. A two-tailed p-value of 0.05 was considered statistically significant. STATA statistical analysis software (version 10) was used (StataCorp, College Station, TX, USA).

3. Results

3.1. Patient demographics

All available data from 542 patients diagnosed with GBM between 1998 and 2010 were included in the analyses. The patient characteristics are shown in Table 1. The median age was 62 years (range 16–89 years). Most patients were male (59%, $n = 322$), and from a major city (69%, $n = 372$ of 536). One-third of the cohort (34%, $n = 185$) was treated in a private hospital. About 33% of patients ($n = 161$ of 480) were born in countries other than Australia (reflecting the multicultural population served by the two institutions), although only 5% ($n = 18$ of 353) required an interpreter at consultation. Most had an ECOG performance status of 0–2 at diagnosis (81%, $n = 311$ of 385). In total, 61 patients (11%) participated in a clinical trial as part of their postoperative management or at recurrence, with 27 patients (5%) participating in a first line trial. For available co-morbidity data (available in approximately 70% of patients), 15% ($n = 59$ of 383) had diabetes, and 51% ($n = 203$ of 399) were current or ex-smokers at the time of diagnosis.

Table 1
Demographics and clinical details of patients with glioblastoma multiforme

Variable	Count	%
Age in years, median (range)	62 (16–89)	
Gender		
Male	322	59.4
Female	220	40.6
IRSAD score		
1–4	141	26.4
5–7	191	35.7
8–10	203	37.9
Missing	7	–
Country of birth		
Australia	319	66.5
Other	161	33.5
Missing	62	–
Residence		
City	372	69.4
Regional/rural	164	30.6
Missing	6	–
Interpreter required		
Yes	18	5.1
No	335	94.9
Missing	189	–
Hospital		
Public	357	65.9
Private	185	34.1
ECOG score		
0–2	311	80.8
3–4	74	19.2
Missing	157	–
Clinical trial		
Yes	61	11.3
No	481	88.7
First line trial		
Yes	27	5.0
No	515	95.0
Diabetes		
Yes	59	15.4
No	324	84.6
Missing	159	–
Smoking		
Never	196	49.1
Past	121	30.3
Current	82	20.6
Missing	143	–
Tumor location		
Lobar – frontal	131	25.1
Lobar – other (±frontal)	273	52.3
Lobar + deep/infratentorial	80	15.3
Deep/infratentorial	19	3.6
Other	19	3.6
Missing	20	–
Tumor diameter		
<3 cm	64	17.7
⩾3 cm	297	82.3
Missing	181	–
Multifocal disease		
Yes	82	16.6
No	413	83.4
Missing	47	–
Operation type		
Craniotomy	414	88.3
Biopsy	55	11.7
Missing	73	–
Extent of resection		
Biopsy only	36	10.2
Partial resection (<50%)	31	8.8
Subtotal resection (50–95%)	150	42.5
Gross macroscopic resection	136	38.5
Missing	189	–
Number of operations		
1	441	81.4
2	76	14.0
3+	25	4.6

IRSAD = Index of Relative Socioeconomic Advantage and Disadvantage.
ECOG = Eastern Cooperative Oncology Group.

3.2. Tumor characteristics and management

Tumor location information was recorded for all except for 20 patients (Table 1). Most patients (77%, $n = 404$ of 522) had a tumor in a lobar location; of these, 131 (25%) had frontal lobe tumors. In most circumstances (82%, $n = 297$ of 361) the maximum tumor diameter was at least 3 cm. Multifocal disease was present at diagnosis in 17% ($n = 82$ of 495). Most patients (88%, n=414 of 469) had a craniotomy rather than a biopsy, and 39% ($n = 136$ of 353) had a gross macroscopic resection. About 19% ($n = 101$) underwent more than one operation for their brain tumor.

3.3. Associations with survival

The median OS for the entire cohort was 7.7 months. Significantly higher median OS was seen in univariable analysis for patients participating in a clinical trial (14.5 compared to 6.3 months, hazard ratio [HR]: 0.46, 95% confidence interval [CI]: 0.34–0.61, $p < 0.001$); patients participating in a first line trial (12.9 months compared to 7.5 months, HR: 0.47, 95% CI: 0.29–0.77, $p = 0.003$); patients with a higher IRSAD score reflecting better SES (9.0 months for decile 8–10 compared to 6.8 months for decile 1–4, HR: 0.74, 95% CI: 0.59–0.93, $p = 0.009$); patients with a frontal lobe tumor location (8.7 months compared to 7.4 months, HR: 0.77, 95% CI: 0.62–0.95, $p = 0.015$); gross macroscopic resection (9.5 months compared to 7.0 months, HR: 0.64, 95% CI: 0.51–0.81, $p < 0.001$); and undergoing more than one operation (31.3 months for 3+ operations compared to 6.0 months for 1 operation, HR: 0.27, 95% CI: 0.17–0.41, $p < 0.001$) (Fig. 1).

The OS was significantly inferior for patients as age increased (HR: 1.05, 95% CI: 1.04–1.06, $p < 0.001$); with worse (3–4) ECOG performance status (3.9 months compared to 9.4 months, HR: 1.90, 95% CI: 1.45–2.49, $p < 0.001$); for those requiring an interpreter (6.1 months compared to 9.0 months, HR: 1.89, 95% CI: 1.16–3.09, $p = 0.011$); those having a biopsy rather than craniotomy (2.8 months compared to 8.4 months, HR: 2.08, 95% CI: 1.55–2.79, $p < 0.001$); and in the presence of multifocal disease (4.7 months compared to 8.4 months, HR: 1.50, 95% CI 1.17–1.92, $p = 0.002$) (Fig. 2).

Gender, country of birth, residence, diabetes and smoking status, public compared to private hospital admission and tumor size did not significantly affect survival outcomes. The HR for death and 95% CI are shown in Table 2.

The four variables that retained prognostic significance for survival outcome in multivariate logistic regression modeling were: clinical trial participation (HR 0.67, 95% CI: 0.46–0.99, $p = 0.042$), age at diagnosis (HR for death 1.04 for each year older, 95% CI 1.03–1.05, $p < 0.001$), ECOG performance status (for ECOG 3–4 compared to 0–2, HR: 1.46, 95% CI 1.08–1.98, $p = 0.014$); and operation type (biopsy compared to craniotomy: HR 1.98, 95% CI 1.40–2.80, $p < 0.001$ (Table 3).

4. Discussion

This large cohort study reviewed prospectively collected data for known and novel prognostic variables affecting survival outcomes in patients with GBM. Our study suggests there may be an effect of participation in clinical trials that is independent of age or performance status according to multivariate analysis. Clinical trials, the cornerstone by which new therapies become "gold standard", benefit not only academic and medical communities but also, in ideal circumstances, the individuals who participate – by providing access to new drugs and ensuring close surveillance and optimal care, regardless of the treatment arm. Participation

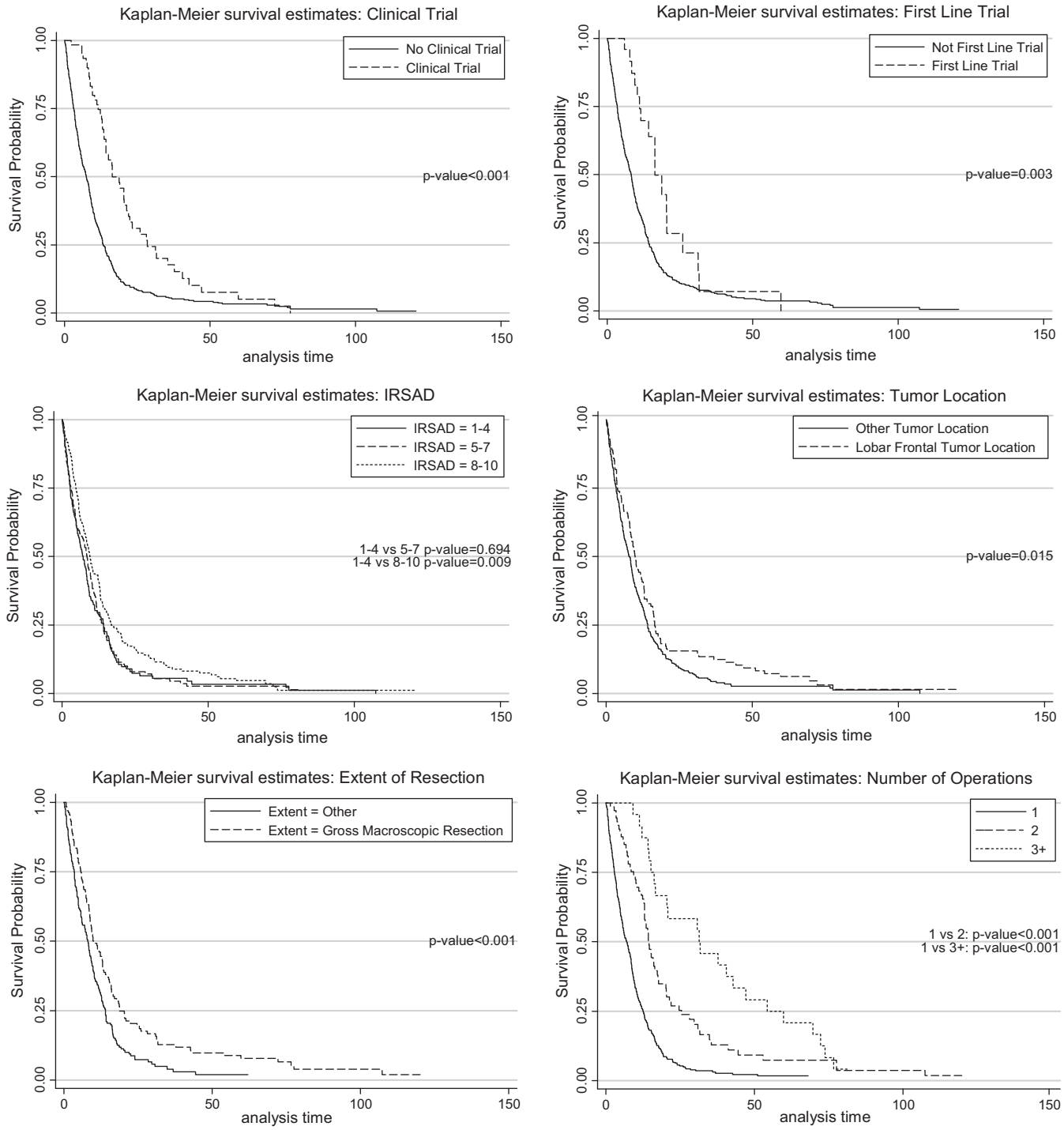

Fig. 1. Kaplan–Meier curves of variables associated with superior overall survival (OS) (univariate analysis) of patients with glioblastoma multiforme showing that participation in a clinical trial, a first line trial, the Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) score, tumor location, extent of resection and number of operations were associated with a longer OS time. Y axis = survival distribution function, X axis = time (months).

in a clinical trial has been reported as improving survival outcomes for patients with other tumor types[7–9] although whether this reflects strict eligibility criteria – for example, excluding patients with a poor prognosis – or a direct benefit from trial participation – remains contentious.[4,10] To our knowledge, such an effect has not been reported previously for patients with GBM.

This research should provide an incentive for cancer centers and patients alike to become involved in brain tumor clinical trials where possible. An 11% participation rate in clinical trials is higher than Australian state averages for trial participation of around 7% regardless of tumor type[11] and thus is a significant achievement for the participating hospitals given that GBM is a relatively rare tumor. Nevertheless, this percentage corresponds to only 61 patients, and therefore larger cohorts should be studied to determine whether this is a reproducible finding.

An obvious limitation which prevents a more robust conclusion about the effect of clinical trial participation is that we were not able to comprehensively assess postoperative treatment including radiotherapy and/or chemotherapy details. While this would have been ideal, the clinical database used for this study did not collect

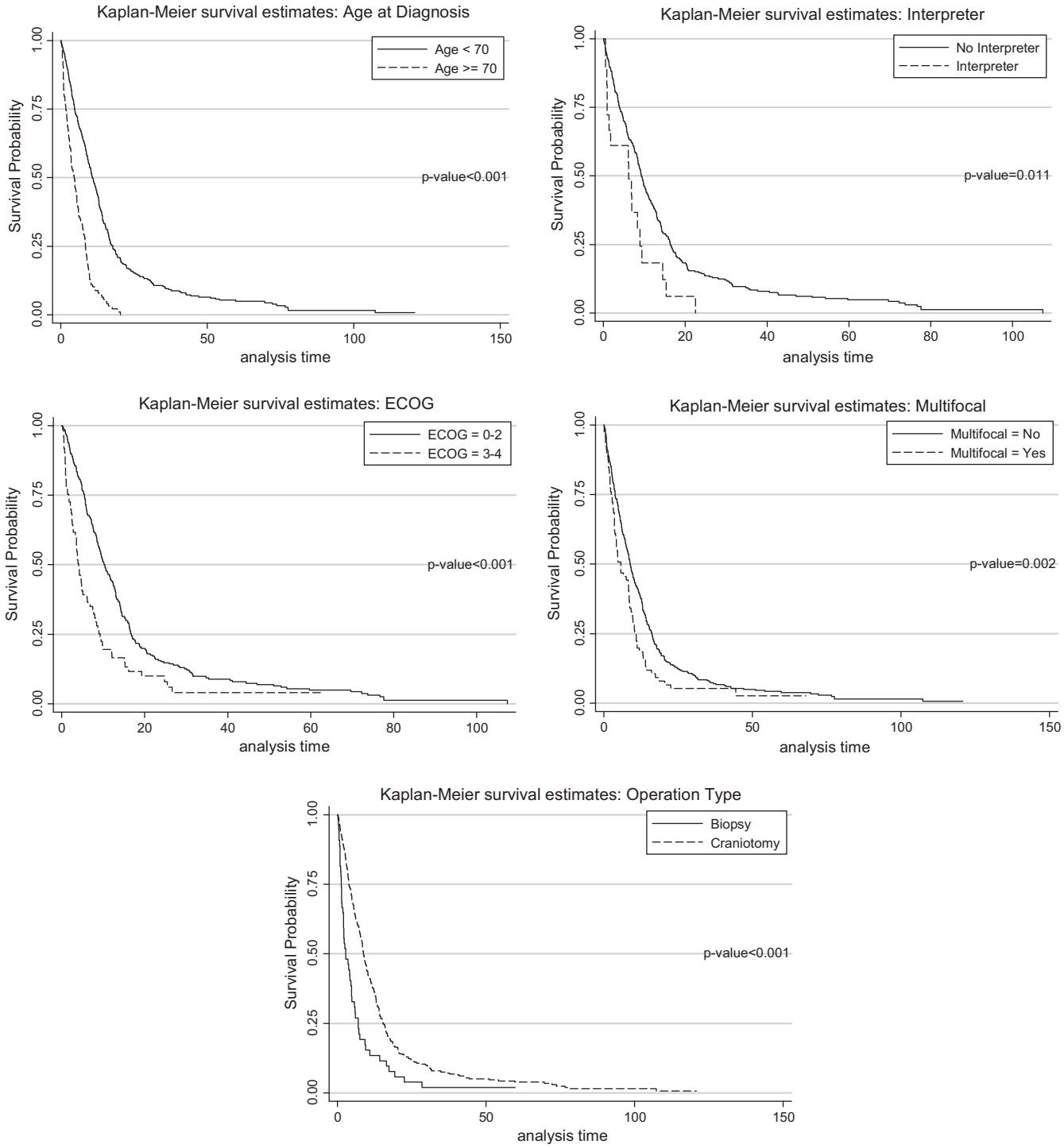

Fig. 2. Kaplan–Meier curves of variables associated with inferior overall survival (OS) (univariate analysis) of patients with glioblastoma multiforme showing that age at diagnosis, presence of an interpreter, Eastern Cooperative Oncology Group (ECOG) score, multifocal disease and operation type were associated with a shorter OS time. Y axis = survival distribution function, X axis = time (months).

any treatment details until 2007. The standard management prior to 2005 in Australia was, for patients with adequate performance status, postoperative radiotherapy alone, reserving temozolomide for recurrent disease. Since 2005 the practice has changed significantly, with well patients under 70 years being given concurrent chemoradiation and 6 months of post-radiotherapy temozolomide, as per the EORTC trial of Stupp et al.[12] We can assume that most patients who were well enough received this therapy; however, without this information being readily available for most patients, we chose not to include treatment details in the analysis. Indeed, the remarkable survival difference between patients participating in a clinical trial and those not, suggests that at least a proportion of patients who did not participate in a trial may have received no postoperative treatment. The 2005 paradigm shift in management, occurring in the years during which the patients in this cohort were cared for, could be seen as a weakness of this study; however, an alternative way of viewing this is that despite changes in "standard" treatments offered over this time, the importance of clinical trial participation was apparent throughout. Nevertheless, it is crucial to ascertain whether the effect of clinical trial participation

Table 2
Univariate analysis of clinical and sociodemographic variables and survival of patients with glioblastoma multiforme

Variable	Level	*n*	Survival months Med (IQR)	HR for death	95% CI	*p*-Value
Age				1.05	1.04–1.06	**<0.001**
IRSAD	1–4	141	6.8 (2.7–13.4)	1.00		
	5–7	191	7.5 (2.4–12.4)	0.96	0.76–1.20	0.694
	8–10	203	9.0 (3.9–15.8)	0.74	0.59–0.93	**0.009**
ECOG	0–2	311	9.4 (4.7–16.2)	1.00		
	3–4	74	3.9 (1.4–8.9)	1.90	1.45–2.49	**<0.001**
Clinical trial	No	481	6.3 (2.6–12.7)	1.00		
	Yes	61	14.5 (11.1–22.7)	0.46	0.34–0.61	**<0.001**
First line trial	No	515	7.5 (2.8–13.5)	1.00		
	Yes	27	12.9 (8.4–18.7)	0.47	0.29–0.77	**0.003**
Tumor location	Other	374	7.4 (2.9–13.4)	1.00		
	Frontal	131	8.7 (3.5–16.2)	0.77	0.62–0.95	**0.015**
Multifocal disease	No	413	8.4 (3.4–14.5)	1.00		
	Yes	82	4.7 (2.2–10.2)	1.50	1.17–1.92	**0.002**
Operation type	Craniotomy	414	8.4 (3.5–14.2)	1.00		
	Biopsy	55	2.8 (1.3–7.0)	2.08	1.55–2.79	**<0.001**
Extent of resection	Other	217	7.0 (2.5–12.7)	1.00		
	Gross macro	136	9.5 (5.6–16.8)	0.64	0.51–0.81	**<0.001**
No. of operations	1	441	6.0 (2.4–11.6)	1.00	0.34–	
	2	76	13.3 (7.5–20.9)	0.42	0.560.17–	**<0.001**
	3+	25	31.3 (15.1–54.2)	0.27	0.41	**<0.001**
Interpreter	No	335	9.0 (3.6–15.2)	1.00		
	Yes	18	6.1 (1.0–8.9)	1.89	1.16–3.09	**0.011**
Country of birth	Australia	319	8.4 (3.4–14.2)	1.00		
	Other	161	8.1 (2.8–14.0)	1.15	0.94–1.42	0.169
Residence	City	372	8.4 (3.5–14.2)	1.00		
	Regional	164	7.2 (2.6–13.2)	1.18	0.97–1.43	0.104
Hospital	Public	357	7.5 (2.8–13.4)	1.00		
	Private	185	8.6 (3.2–14.4)	0.85	0.70–1.03	0.089
Diabetes	No	324	8.1 (3.4–14.2)	1.00		
	Yes	59	8.4 (3.5–12.9)	1.25	0.94–1.67	0.126
Smoking	Never	196	8.1 (3.4–14.2)	1.00		
	Ever	203	7,7 (3.1–14.0)	1.11	0.90–1.37	0.331
Tumor diameter	<3 cm	64	9.7 (4.6–14.0)	1.00		
	⩾3 cm	297	7.5 (3.1–14.0)	1.13	0.84–1.52	0.408
Gender	Male	322	8.7 (3.1–14.2)	1.00		
	Female	220	6.5 (2.9–13.0)	1.06	0.88–1.28	0.517

p Values in bold indicate significant differences.
CI = confidence interval, Gross macro = gross macroscopic resection, HR = hazard ratio, Med (IQR) = median (interquartile range), ECOG = Eastern Cooperative Oncology Group performance status at diagnosis, IRSAD = Index of Relative Social Advantage and Disadvantage.

Table 3
Multivariate Cox regression survival analysis of clinical and sociodemographic variables and survival of patients with glioblastoma multiforme

Variable	HR for death	95% CI	p value
Age	1.04	1.03–1.05	**<0.001**
ECOG 3–4	1.46	1.08–1.98	**0.014**
Clinical trial	0.67	0.46–0.99	**0.042**
Operation type – biopsy	1.98	1.40–2.80	**<0.001**
IRSAD			
1–4 *vs.* 5–7	1.16	0.85–1.58	0.340
1–4 *vs.* 8–10	0.92	0.68–1.23	0.558

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group performance status at diagnosis, HR = hazard ratio, IRSAD = Index of Relative Socioeconomic Advantage and Disadvantage. *p* values in bold indicate significant differences.

would remain sound with more comprehensive treatment data. The revised dataset does now include comprehensive treatment details such that future analyses will allow inclusion of postoperative treatment strategies with the additional benefit of retrospective chart review adding these details retrospectively for already-included patients.

Our study represents the catchment area of two co-located and related Victorian hospitals; therefore, one cannot make a definitive statement about whether the impact of clinical trial participation and other examined variables on survival outcomes is applicable to the remainder of Australia and internationally. It is a strength of this study that patients are managed by the same doctors, all of whom have a subspecialty interest in brain tumors, and are managed by consistent protocols – thus, analysis is not confounded by inconsistent approaches and varying quality of treatment across the patient cohort. However, it would be ideal to conduct a larger study looking at the impact of clinical trial participation, as well as the sociodemographic variables, in a wider and broader cohort of patients with brain tumors in Australia and other countries. These patterns may change depending on the location of participating hospitals – however, based on many of our demographic and outcome findings mirroring available literature, we believe this to be a cohort that well-represents patients with GBM.

While the country of birth and requirement for an interpreter were not independently significant prognostic factors, there are nevertheless some concerns arising from this study, in that only one patient enrolled on a clinical trial was listed as requiring an interpreter. In ideal circumstances language should not be a barrier to clinical trial participation. There may well be other cultural factors that preclude clinical trial participation. It is well documented that minority groups are poorly represented in clinical trials around the world[13–15]; this is an ongoing concern given this study's finding of the potential positive benefits of trial participation. As such, being aware of these variables is crucially important in understanding the patterns of care for patients with GBM, and cancer action plans and research methods must take the demographics of a population into consideration.

The association between socioeconomic status and outcomes has been documented in multiple studies for patients with other tumor types, with those from a lower socioeconomic group having poorer cancer-related outcomes.[16–22] This may partly be related to co-morbidities such as obesity, smoking and diabetes being more prevalent in lower socioeconomic groups; however, notably in our cohort there was no significant effect of smoking status and diabetes on outcomes. Many other reasons have been postulated as to why those from lower socioeconomic groups may have inferior outcomes. Some, including screening availability and adherence,[21] do not relate to patients with brain tumors, who tend to present acutely and for whom no screening test is available. Our study is the first to investigate in an Australian cohort of patients with GBM, whether more "disadvantaged" groups as per the IRSAD may be faced with an inferior outcome, and no difference was found. This is reassuring, as it would suggest that those with brain tumors – at least in this patient cohort – do not have outcome discrepancies based on socioeconomic background. This is important as international research has suggested some associations between SES and outcomes in patients with gliomas.[23–25] Ultimately a larger Australia-wide study would be ideal to determine whether there are discrepancies in survival based on SES.

We have also documented that age, performance status, type of operation and resection extent are strongly related to length of survival and outcomes for patients with GBM. These finding are supported by extensive literature.[26–28] The identification and confirmation in our cohort of these well-established prognostic variables lends strength to this study, suggesting that our cohort is representative of patients with GBM and that our novel findings are unlikely to be specific to this patient cohort.

There were several other limitations to this retrospective study. First, the data are from only two hospitals, and thus may not be necessarily representative of the entire population in this state and country. However, all deciles of the IRSAD score were evenly represented, suggesting patients from a a broad range of SES and given the tertiary nature of care and the broad hospital catchment area – including approximately one-third of patients being from regional or rural areas – we believe this cohort of patients to be representative of the Australian population. Further, the identification and confirmation of well-established prognostic variables reinforces this being a representative cohort. Second, the IRSAD score itself has some limitations; but remains an objective and validated means by which SES is gauged. There were also missing data for some variables that may lead to some bias in the results. This is largely due to a new, more comprehensive database being established from 2007 onwards and thus some missing data fields from before this time. The missing data have been subsequently added to the database where available, but this was not possible in all cases.

This research demonstrates the potential utility of clinical trials in improving survival in patients with GBM. Our research reinforces the benefit of offering and providing clinical trials to patients with GBM; the impetus to continue to support clinical trials in oncology; and will assist in informing future directions in malignant glioma research.

Conflicts of interest/disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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