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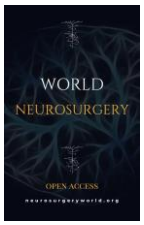

Research Article

Part 1 - Do Less Harm: A Quantitative Analysis of Morbidity and Mortality Following Treatment of Glioblastoma in the Elderly and the Development of a Clinical Prognostic Tool

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ABSTRACT

Objective: Treating glioblastoma (GB) in elderly patients requires balancing survival advantage against quality of life (QOL). Mortality outcomes are well established, but information on post-treatment QOL is limited. This study examines post-operative QOL in elderly patients, employing functional independence (FI) as a proxy for morbidity, and uses both morbidity and mortality data to develop a clinically relevant prognostic tool.

Methods: Records of patients aged ≥ 60 years who underwent surgery for a histologically confirmed GB at a single center between August 2000 and September 2018 were retrospectively reviewed. Loss of FI, measured by the Karnofsky Performance Status (KPS), was defined as the first documented loss of independence with activities of daily living after surgery. Pre-operative factors associated with morbidity and mortality were assessed with multivariable analyses. A prognostic tool for morbidity and mortality was developed using a cross-validation (hold-one-out) method.

Results: The cohort of 352 patients (mean age 69.1 years) had a median survival of 7.1 months. Median FI was 1.3 months, 2.7 months and 0 months in the total cohort, resection and biopsy subgroups, respectively. In the ≥ 75 age group, only 8% of patients retained FI post-operatively, compared to 74% in the 60-64.9 age group. Pre-operatively, increasing age ($p = 0.002$), decreasing KPS scores ($p < 4 \times 10^{-7}$) and the presence of bilateral tumors ($p = 0.02$) predicted reduced FI.

Conclusion: In biopsied patients age 75 or older, FI was neither retained nor regained post-operatively. Therefore, surgical intervention in this sub-population likely adds to patients' physical and mental burden prior to death. Given the potential for harm, use of the prognostic tool during the consent process to estimate individual morbidity and mortality may better facilitate patient-centered care.

1. Introduction

Glioblastoma (GB) is the most common malignant primary brain tumor in adults, with the median age at diagnosis in the United States being 66 [1]. Life expectancy is markedly reduced, with a median survival time of 14.6 months in a young, medically optimized cohort that receives gold standard treatment, i.e. maximal surgical resection and chemoradiotherapy, a figure that has increased only 2.1 months in the last two decades [2, 3]. Increasing age and lower pre-operative performance status are both independent negative prognostic indicators for survival in GB and are both used as differentiators in modern treatment guidelines [1, 4-8]. Current 1-year survival rates in the 55-64, 65-74 and 75+ age groups are reported as 48.2%, 32.5% and 14.1%, respectively [1]. In patients aged 65, a Karnofsky performance status

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(KPS) score of < 70 has been shown to confer a survival time of just 2.8 months, while those with a KPS score of ⩾ 90 survive an average of 17.2 months [5, 6, 8]. Optimized treatment in this older, but clinically well cohort, can further extend survival to 21.8 months [6].

Treatment variance observed in the older and frail cohorts is largely attributed to a higher rate of comorbidities, lower physiological reserve and concern for treatment related toxicity [9-11]. Determining which elderly patients may benefit from treatment is becoming increasingly important as the disease burden of GB in the elderly is expected to increase. The World Health Organization estimates the proportion of those aged over 65 to double by 2050 [12].

The current outcome measure that informs treatment guidelines is mortality data. However, there is no data demonstrating whether a prolonged survival translates into an improved quality of life (QOL). Sagberg [13] and Jakola [14] studied the subjective patient perspective and identified multiple physical factors (e.g., fatigue), new neurological deficits, and psycho-social factors (e.g., the intense scheduling of chemoradiotherapy), as well as existential distress, which can all impact on overall subjective well-being during treatment [13, 14]. Arvold [15] used post-operative hospitalization burden as a surrogate for morbidity and showed that 22% of their elderly cohort spent a quarter of their remaining life as inpatients.

These results contribute essential knowledge for optimal and holistic management of GB. However, they are unable to provide guidance on whether the post-treatment QOL will be of a standard that justifies invasive surgical treatment. This study addresses that knowledge gap by evaluating post-operative morbidity, defined as loss of independence with activities of daily living (ADLs), and mortality in elderly patients with GBs. A clinically relevant prognostic tool for use during pre-operative consent has been developed from predictive modelling of the study's morbidity and mortality data.

2. Methods

2.1. Cohort

This is a single center retrospective cohort study of all patients aged 60 years and older who were operated on at the Department of Neurosurgery at Wellington Regional Hospital (WRH; Wellington, New Zealand) between August 2000 and September 2018. All patients with a histologically confirmed diagnosis of a supratentorial glioblastoma from a biopsy, sub-total or gross total resection, and without a concurrent cause of death, were included. This study was approved by the Capital & Coast District Health Board (CCDHB) Clinical Audit and Research Committee, the CCDHB Research Advisory Group Māori, and the New Zealand Ministry of Health - Health and Disability Ethics Committee.

Clinical trials on "elderly" patients range from 60 to 80 years and older [16]. This study selected patients aged 60 years and older in order to identify the cusp at which increasing age and medical fragility impacts upon post-operative outcomes. For the descriptive analysis only, the cohort was divided into three groups (60-64.9, 65-74.9, and 75 and above) following visual analysis of Kaplan-Meier curves.

2.2. Karnofsky Performance Status Score

Pre-operative clinical status for all patients was assessed using the KPS score [4]. Scores were based on a review of paper and electronic clinical records, from time of presentation to either the patient's home hospital or WRH. Reviewers were blinded to patient outcome.

2.3. Functional Independence

Functional independence (FI) is a proxy for morbidity and, for this study's purposes, is defined as independence with ADLs. ADLs are six fundamental skills required to independently care for oneself, including the ability to feed, dress, bathe, and toilet oneself, mobilize independently and retain urinary and bowel continence [17]. Post-operatively all patients were assessed by occupational therapists or physiotherapists to determine whether they had retained or regained FI. Upon achieving independence with ADLs patients were discharged home on what was considered Day 1 of FI. Subsequently, WRH, home hospital, clinic, general practice, rest home and hospice records were reviewed for the first documented evidence that the patient had permanently lost their FI. The day before that date was considered their last day of FI. Transient losses of FI (e.g., seizure activity requiring a short stay in hospital) were subtracted from the patient's total length of FI. Patients that did not regain FI post-operatively were recorded as having zero days of FI.

2.4. Volumetric Assessment of Tumors

Volumetric assessment of tumors was performed using 3D Slicer 4.11 software and the segment editor and quantification/segment statistics features. Magnetic Resonance Imaging (MRI) scans uploaded into a Picture Archiving and Communications Software (PACS) package were used, which excluded patients treated prior to mid-2008, as they only had film stock available. Preference was given to post-contrast axial T1 images, but any post-contrast T1 Stealth, fluid-attenuated inversion recovery or T2-weighted axial images were used if necessary.

2.5. Chemoradiotherapy

Radiotherapy and chemotherapy data were obtained from digital hospital records and were corroborated with radiation therapy software data sources including Aria (v13.7) and Mosaiq (v2.64) from the respective treatment centers. Patients who received chemoradiotherapy abroad and did not have data available for collection were counted as not having received it.

2.6. Statistical Analysis

Statistical analysis was undertaken to: i) establish the comparability of this study's cohort and results with those of other international centers' mortality studies, ii) quantify morbidity outcomes and identify pre-operative variables associated with both mortality and morbidity for the purposes of clinical decision-making, and iii) develop a prognostic tool for the estimation of the probability that a patient will achieve certain positive outcomes after the operation. To establish comparability with the results of other studies that have examined mortality, a Cox proportional hazard model was used for the number of days to death

(DTD) with the (quasi-) continuous variables, AGE (in years), KPS and tumor size (in cm^3) and the binary variables for whether the tumor was multifocal (MULTI) and/or bilateral (BILAT): (1 = yes) and (0 = no). These variables were included without interactions. A median-regression model was also used, which addresses the same question in an alternative manner.

To help inform a clinician's decision on whether to offer an operation, a median-regression analysis was performed to assess the overall effect of pre-operative variables on outcomes. This takes into account the flow-on effects of post-operative treatments. The outcome variables were DTD and days of functional independence (DFI), and the pre-operative variables selected were AGE, KPS, MULTI and BILAT. To develop a prognostic tool for use by clinicians and patients during the consent process, four relevant post-operative achievements for patients were identified:

i) The patient would have 1 or more DFI post-operatively.
ii) The patient would have 90 or more DFI post-operatively.
iii) The patient would have 90 or more DTD post-operatively.
iv) The patient would have 180 or more DTD post-operatively.

Logistic regression was then used to develop models that provide point and 95% confidence interval estimates of the probabilities of each of these four events. The 'predictors' are pre-operative variables readily available in clinical practice, namely AGE, KPS, MULTI and BILAT. The focus was to develop applicable models that performed well in practice, as assessed using 'hold-one-out' cross-validation. The four prognostic models were chosen by simultaneously studying the Brier score, the area under the sensitivity-specificity curve, and the likelihood function, and by constraining the form of the models to give estimates of probability that vary monotonically when input variables are varied monotonically [18].

3. Results

3.1. Patient Characteristics: Demographics and Mortality

Three hundred and fifty-two consecutive patients [134 female (38%) and 218 male (62%)] with a mean age of 69.1 years (SD ± 6.2) and an age range of 60-87 years were included. Patient characteristics are summarized in (Table 1). The median pre-operative KPS was 60 (IQR 40-80). Fifty-two patients had multifocal GBs (15%), and 35 (10%) had bilateral tumors. Tumor volumes were calculated from 255 patients as the remaining patients had imaging prior to 2008 on film stock. Median tumor volume was 34.8 cm^3 and the range was 0.1-143.9 cm^3. Total gross resections, subtotal resections and biopsies were performed in 95 (27%), 192 (55%), and 65 (18%) patients, respectively. Post-operatively, 158 patients (45%) received chemoradiotherapy and a further 88 patients (25%) had radiotherapy alone. A second tumor-debulking surgery was performed in 31 patients (9%), and a third in a further 2 patients (0.6%).

Table. 1. Cohort characteristics.

Cohort size	352
Age range (years)	60 - 87
Mean age ± SD	69.1 ± 6.2
Median age	68
60 - 64.9 years	27%
65 - 74.9 years	53%
75+	20%
Gender	
Male	62%
Female	38%
Median KPS (IQR)	60 (40 - 80)
KPS < 70	61%
KPS ≥ 70	39%
Biopsy	18%
Subtotal resection	55%
Gross total resection	27%
Median MTD	
Biopsy	3.1
Resection	8.5
Total cohort	7.1
Multifocal tumors	15%
Bilateral tumors	10%
Radiotherapy alone	25%
Chemoradiotherapy	45%
Volume of tumor (cm^3)	(n = 255)
Mean ± SD	40.5 ± 29.2
Median	34.8

KPS: Karnofsky Performance Status, MTD: months to death.

Median months to death (MTD) for the total cohort was 7.1, which increased to 8.5 for those who received a resection, but fell to 3.1 for those who underwent a biopsy. Life expectancy fell further in the biopsy subgroup for those aged 75 years and above to 2.4 months. One patient was alive at the end of the study, and one had moved back to Britain at an unspecified date. Their dates of death were taken to be the final date of statistical analysis, which would not introduce significant error.

3.2. Comparability of Predictive Factors for Mortality

3.2.1. Using Pre- and Post-Operative Variables

A Cox regression analysis was performed on the 255 patients with tumor volume information and looked at pre-operative factors and DTD (see Table 2). Pre-operative variables include patient characteristics such as age and KPS, as well as tumor characteristics such as multifocality, bilaterality and tumor volume. We conclude that increasing age (p = 0.0004), declining KPS (p = 0.007), the presence of a multifocal GB (p = 0.002) or a bilateral tumor (p = 0.001) are all associated with a poorer prognosis, which is concordant with the literature [3, 5, 6, 8, 9, 19-21]. There is conflicting published evidence regarding tumor size affecting overall survival and there is insufficient evidence from this study to support an association of tumor volume with mortality [6, 19].

Table. 2. Multivariable Cox regression analysis of pre-operative factors associated with DTD.

Factor	z score	*p* value
Age	3.535	0.0004***
Karnofsky Performance Score	-2.720	0.007**
Multifocal tumor	3.040	0.002**
Bilateral tumor	3.284	0.001**
Tumor volume	0.868	0.385

** p value < 0.01, *** p value < 0.001, DTD = days to death.

Pre- and post-operative variables associated with a shorter life expectancy were studied in a Cox regression analysis. The analysis shows that peri-operative factors of having a biopsy (p = 0.0001), a bilateral tumor (p = 0.002), and not receiving radiotherapy ($p = 4 \times 10^{-8}$) or chemoradiotherapy ($p = 2 \times 10^{-16}$), were associated with a decrease in DTD. With the inclusion of post-operative variables in the multivariable analysis, all the pre-operative variables lost their statistical significance except for the presence of a bilateral tumor.

3.2.2. Using Pre-Operative Variables Only

Table 3 gives the results of the median-regression analysis for the effects of pre-operative variables on mortality, which take into account any flow-on effect of post-operative treatments. These results are to assist with pre-operative decision-making using only readily available data. For example, when considering patient age, a best point estimate is that for each year increase in age there is a decrease of 7.7 (CI 5.2-9.8) in the median number of DTD post-operatively. Similarly, with KPS scores having stepwise increments of 10, each step increase in KPS score is estimated to lead to an increase of 18.8 (CI 9.9-33.1) in the median DTD that could be expected. Likewise, the presence of a bilateral tumor is estimated to result in a decrease of 113 days (CI 39-152) in the median DTD.

Table. 3. Median-regression analysis of pre-operative variables associated with DTD.

	Estimate	Lower Limit	Upper Limit	*p* value
Age	-7.72	-9.75	-5.21	7.4×10^{-6}***
Karnofsky Performance Score	1.88	0.99	3.31	0.006**
Multifocal tumor	-29.72	-80.70	15.40	0.23
Bilateral tumor	-113.22	-152.43	-39.41	5.7×10^{-4}***

** p value < 0.01, *** p value < 0.001, DTD = days to death.
Limits are of a 95% confidence interval.

3.3. Patient Characteristics: Functional Independence/ Morbidity

Information about functional independence was available in a reduced cohort of 322. Morbidity could not be ascertained for 30 patients due to: patients moving country, no next of kin (NOK) listed, no contact information for NOK, general practitioners (GPs) declining to share patient's personal information, paper records being lost when patients moved practices or documents being securely destroyed post-death by their GP practice. The single living patient was functionally independent at the end of the study, so their days of FI, along with the patient lost to follow up due to moving overseas, were estimated using the date of the final statistical analysis. Table 4 compares mean and median MTD and months of functional independence (MFI) by surgery type. Whilst the total cohort had a median MTD of 7.1, the median MFI was only 1.3. Patients who had resections had a median MFI of 2.7. However, for those who had a biopsy, their median MFI and even DFI were zero. Overall, 41% of the entire cohort's patients had zero days of FI.

Table 4. Months to death (MTD) versus months of functional independence (MFI).

	MTD (n = 352)	MFI (n = 322)
Mean	11.0	4.8
Median	7.1	1.3
Biopsy, mean	5.8	1.2
Biopsy, median	3.1	0.0
Resection, mean	12.1	5.7
Resection, median	8.5	2.7

The breakdown of FI results by age group and surgery type is displayed in (Table 5). In the youngest group, aged 60-64.9, over one third (36%) of patients were dependent post-op despite potentially having maximal resection and chemoradiotherapy. In the oldest group, aged 75 years and above, over half (57%) of patients had zero DFI, also regardless of treatment type. The age groups were divided further by surgery type and the findings suggest that the higher-than-expected percentages of patients with zero days of FI is primarily driven by poor outcomes in patients who underwent biopsies. In the youngest and oldest age groups, 72% and 92% of patients had zero days of FI after biopsy, respectively. However, if patients received maximal resection and were young, then only 26% were dependent post-operatively. In the oldest group, maximal resection enabled 50% of patients to retain or regain their post-op FI.

Table. 5. Patients with zero days of functional independence by surgery type.

Age Range	Proportion	Percentage
Total cohort		
60 - 64.9	30/84	36%
65 - 74.9	64/170	38%
75+	39/68	57%
Biopsy		
60 - 64.9	13/18	72%
65 - 74.9	20/32	63%
75+	11/12	92%
Resection		
60 - 64.9	17/66	26%
65 - 74.9	44/138	32%
75+	28/56	50%

Mortality data from (Table 1) and morbidity data from (Table 5) are plotted in Kaplan-Meier curves to more easily appreciate the changes in both outcomes by age group and surgery type (Figure 1). The Kaplan-Meier curves for patients receiving a biopsy are notable for the almost global loss of post-operative FI, with 71% of biopsied patients dependent post-op. None of the 12 biopsied patients aged 75 and above survived longer than 4 months. Even in the youngest sub-cohort receiving a biopsy, less than 6% survived longer than 7 months. The curves for patients who received a resection demonstrate improved morbidity. However, it was still severe even in the youngest group, where 50% lost FI by 4 months post-operatively.

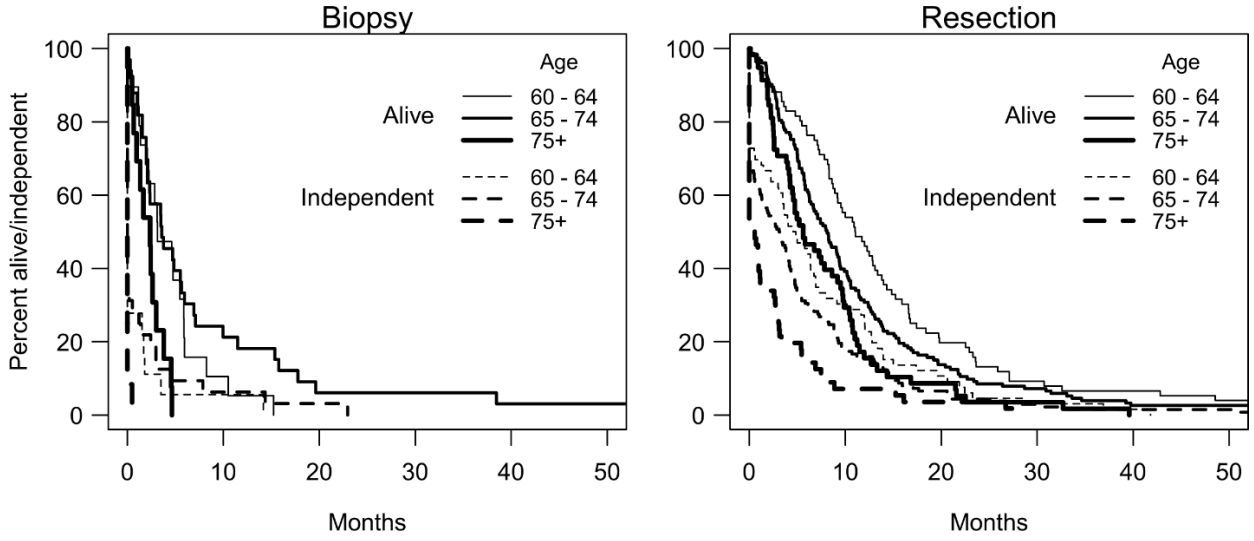

Fig. 1. Kaplan-Meier curves for biopsy and resection comparing mortality (percent alive) versus morbidity (percent independent) by age group.

3.4. Pre-operative Variables Associated with Morbidity

Table 6 gives the results of the median-regression analysis for the effects of pre-operative variables on DFI, with these effects accounting for any flow-on effect of surgery and post-operative treatment. For example, when considering patient age, a best point estimate is that for each year increase in age there is a decrease of 3.5 (CI 2.0-6.1) in the median number of post-op DFI that can be expected. Similarly, with KPS scores having stepwise increments of 10, we estimate that each step increase in KPS score would lead to an increase of 16.5 (CI 9.7-21.2) in the median DFI that could be expected. Likewise, the presence of a bilateral tumor is estimated to result in a decrease of 42 days (CI 2-89) in the median DFI post-operatively.

Table. 6. Median-regression analysis of pre-operative variables associated with DFI.

	Estimate	Lower Limit	Upper Limit	*p* value
Age	-3.52	-6.12	-2.00	0.002**
Karnofsky Performance Status	1.65	0.97	2.12	3.40×10^{-7}***
Multifocal tumor	-9.95	-38.86	18.90	0.52
Bilateral tumor	-42.23	-88.79	-2.29	0.02*

* *p* value < 0.05, ** *p* value < 0.01*** *p* value < 0.001, DFI = days of functional independence.
Limits are of a 95% confidence interval.

3.5. Predictive Tool for Post-operative Morbidity and Mortality

Predictive models were developed to estimate the probabilities of each of the four outcomes. Each model has the logistic form:

$$\log[P/(1\text{-}P)] = b_0 + b_1 \times \text{AGE}^3 + b_2 \times \text{KPS}^3 + b_3 \times \text{MULTI} + b_4 \times \text{BILAT} + b_5 \times \text{KPS}^3 \times \text{MULTI}$$

where P is the probability of the outcome. Each is a 'generalized linear model' fitted to the data using the glm() function of R. The coefficients, rounded to 3 or 4 significant figures, are shown in (Table 7). An elementary model would have AGE and KPS appearing linearly and would not have a term relating to an interaction between KPS and MULTI. This study's models were developed to maximize predictive ability as judged by internal validation: raising AGE and KPS to the power of three and including the interaction term improved the measures of performance. Table 7 also shows 95% confidence intervals for accuracy expressed as 1 minus the Brier score.

Table. 7. Coefficients in predictive models for the four outcomes (rounded).

	i	ii	iii	iv
Coefficient	DFI ≥ 1	DFI ≥ 90	DTD ≥ 90	DTD ≥ 180
b_0	-1.334	-1.101	-2.794	-1.732
b_1	0.00000422	0.00000551	0.00000520	0.00000494
b_2	-0.00000241	-0.00000217	-0.00000197	-0.00000139
b_3	0.820	1.831	1.322	1.306
b_4	0.950	1.474	1.694	1.417
b_5	-0.00000341	-0.00000687	-0.00000721	-0.00000451
Brier accuracy of P (95% CI)	[0.77, 0.80]	[0.77, 0.82]	[0.82, 0.87]	[0.76, 0.80]

The models are implemented online at (www.GBMTool.com). This website uses responsive design to be useable on both desktops and mobiles.

4. Discussion

This novel study is the first to quantify post-operative morbidity alongside mortality in elderly patients with GBs. If is also the first to identify pre-operative predictive variables that affect post-operative FI and to develop a clinically relevant prognostic tool for both outcomes. Initially, patient, tumor and surgical characteristics and mortality outcomes were compared against international cohorts to ensure generalizability of morbidity results with other developed nations' populations. This cohort is the second largest published elderly GB cohort and has a slightly younger mean age, which was intentional, to allow the data to demonstrate the age at which post-operative morbidity and mortality start to decline [5, 8, 19, 20]. Other demographics are also similar except that this cohort has lower pre-operative KPS scores (61% had KPS < 70%), a higher number of multifocal tumors (15%) and a considerably higher number of patients receiving chemoradiotherapy (45%). The overall MTD in the cohort is 7.1 months, and while the published median overall survival ranges from 4.2 to 8.6 months, the variation is mainly attributable to inclusion or exclusion of biopsied patients. The multivariable analysis identifies age, KPS, tumor multifocality and the presence of a bilateral tumor as being associated with mortality, which is also in keeping with the literature [3, 5, 6, 8, 9, 19, 20]. Factoring in the slightly younger cohort, low KPS scores, moderate numbers of biopsies and aggressive rates of chemoradiotherapy, this study's post-operative mortality statistics compare favorably with those from international cohorts [5, 8, 19, 20].

While surgical outcomes in this cohort are comparable in terms of length of survival, this study found that post-operative morbidity is more profound than previously reported. In the resection subgroup, the median MTD was 8.5, but the median MFI was only 2.7. In comparison, the biopsy subgroup had a median MTD of 3.1, but a median MFI of 0. Patients aged 75 years and older with unfavorable KPS scores and tumor characteristics and who were only considered for a biopsy, had an even shorter median MTD of 2.4 and were unlikely to retain or regain FI post-operatively. Given the results for this subcohort, surgeons should consider communicating to patients that: i) the benefit of surgery is isolated to a tissue diagnosis, ii) an operation may increase their physical and psychological burden and, iii) that death will likely occur prior to recovering from their operation.

Pre-operative variables that significantly influenced post-operative morbidity in this cohort include increasing age, decreasing KPS and the presence of a bilateral tumor [13-15]. Increasing age is a well-established negative prognostic factor for mortality [3, 5, 8-10, 19, 20]. However, the impact of age on morbidity is less well-understood. The proportion of patients experiencing zero DFI rose from one-third in the 60-64.9 age group to over half in the 75+ age group, regardless of surgery type. A similar overall trend was seen in a Canadian cohort study of GB cases where 21.9% of those aged 60-69 spent their entire survival time as an inpatient and never returned home [22]. Another study using the Surveillance, Epidemiology, and End Results registry data from 1999-2007 showed that 22% of those aged 65 and over who underwent GB treatment spent at least a quarter of their remaining lives as inpatients [15]. Although the morbidity data is concordant with the literature, this study's additional quantitative analyses of FI provide insight into the expected age-dependent decline in post-operative morbidity.

Performance status influences both mortality and morbidity, as well as playing a role in treatment planning [5, 6, 8, 9, 19, 20]. An Australian study looking at GB patients ≥ 74 years of age showed that an Eastern Cooperative Oncology Group Performance Scale (ECOG PS) 0-1 was associated with a median overall survival of 11.8 months, which dropped to 6.3 months for those that had an ECOG PS of 2-3 [23]. Another study

looking at GB patients ≥ 65 years of age, showed that a KPS of 70 or below was associated with a survival time of approximately 7.3 months, rising to 21.8 months with a KPS of 90 [6]. This study's results suggest that for each incremental increase in pre-operative KPS score, an increase of 18.8 median DTD can be expected post-operatively. A higher KPS also improves morbidity - each incremental increase in KPS score is estimated to result in an increase of 16.5 DFI post-op. This relationship has been similarly demonstrated by Arvold [15] who showed that a Modified Charleston Comorbidity score of 0 versus ≥ 2 resulted in 63.5% instead of 11.4% (respectively) of patients spending less than a quarter of their lives hospitalized [15].

Tumor characteristics such as multifocality and bilaterality have been associated with a lower overall survival due, in part, to decreased use of conventional treatment. Prior studies demonstrate that multifocal tumors conferred a reduction in median overall survival by 4.5 months and bilateral tumors were associated with a hazard ratio of 1.9 (1.3-2.9, $p < 0.001$) for lower overall survival [8, 21]. In this cohort, the presence of a bilateral tumor led to an estimated decrease in 113 median DTD, independent of post-operative factors. Importantly, when post-operative treatments were included in the multivariable analyses of survival, bilaterality was the only pre-operative predictive variable that maintained statistical significance. With regard to morbidity, the presence of a bilateral tumor, but not multifocality, reached statistical significance for prognostication. It is associated with an approximate decrease of 42 DFI post-op.

There is a lack of robust data supporting the use of tumor size for prognostication; however, many studies use tumor area or diameter calculated in a single slice, which is not an accurate measure [24-26]. This study uses volumetric tumor assessment, which is considered to be the gold standard method for evaluating tumour size [27]. This study's data did not show that tumor volume in isolation influenced either overall survival or DFI. Alternate tumor characteristics observed on MRI, such as volume of necrosis and peritumoral edema, may prove to be more important than tumor size [24-26] and theoretically, tumors in eloquent areas may prove more difficult surgical targets and therefore be associated with worse outcomes. However, studies that recorded tumor location were also unable to demonstrate its association with overall survival [6, 19].

4.1. Prognostic Tool

This study enabled the development of a prognostic tool to estimate post-operative morbidity and mortality based on patients' age, clinical status and tumor characteristics (www.GBMTool.com). Currently, the published data that informs clinicians' decisions to operate and subsequent consent discussions are population-level mortality outcomes. Even when considering survival length in isolation, no tool previously existed to enable surgeons to apply that global knowledge to individual patients. Access to a prognostic tool that includes both morbidity and mortality might assist clinicians in evaluating whether a patient will benefit from surgical intervention. The tool can also be employed to facilitate the consent process by setting realistic expectations for the patient, thereby empowering them to make a decision better tailored to their priorities.

4.2. Limitations

The limitations of this study include that it is both retrospective and observational, which can make it difficult to isolate the effect of pre-operative factors from post-operative treatments, as they were only offered to those who did well enough peri-operatively to receive them.

Patients were operated on at a single institution, which can reduce generalizability of results due to small sample sizes, unique patients/staff/protocols, and a lack of a diverse population. WRH is a regional tertiary service, providing neurosurgical treatment to a quarter of New Zealand by land mass. This area includes a diverse and sizeable population and enabled the recruitment of the second largest elderly GB cohort published internationally [5, 8, 19, 20]. Ten consultant neurosurgeons and countless rotating senior training registrars were responsible for operating on, and caring for, our cohort. Nine out of the ten consultants were trained abroad, and all senior trainees gain surgical experience rotating through tertiary facilities across Australia and New Zealand. This breath of international experience helped reduce the potential for divergent practice.

The tumor volume data is incomplete as scans were digitized onto WRH's current PACS halfway through the study cohort. Therefore only 72% of images were suitable for volumetric assessment. The reduction in sample size might have contributed to the lack of a statistically significant result when testing for associations between tumor size and outcomes.

Not all of the cohort received the gold standard treatment as established by Stupp [2] because this study's intake predates its development by five years [2]. While this might be expected to result in worse outcomes, the study outcomes are still comparable to more recent and similarly aged international cohorts. A possible explanation is that this cohort had more aggressive rates of chemoradiotherapy at 45% in comparison to the aforementioned cohorts, which had chemoradiotherapy rates ranging from 17% to 29% [3, 5, 8, 19, 20].

This study did not have an independent cohort for external validation of the prognostic tool. To compensate for this, a method of hold-one-out cross validation to internally validate the results was used.

5. Conclusion

This novel study quantifies post-operative morbidity and mortality in elderly patients with GBs and identifies key pre-operative variables that influence both outcomes. While the short survival times for patients with GBs are well documented, the significantly shorter length of time patients retain post-operative FI has not previously been reported and reveals how profoundly debilitating GB morbidity can be. Notably, those aged 75 years and over who underwent a biopsy alone had a median of zero days of FI. This suggests that beyond providing a tissue diagnosis, the benefit of invasive treatment in this subcohort of elderly patients with unfavorable clinical status and tumor characteristics, was limited. Surgical intervention may have instead conferred additional physical and psychological burdens on these patients prior to death.

The FI and survival data from the entire cohort enabled the development of a prognostic model that gives individualized pre-operative predictions of post-operative morbidity and mortality to support the informed consent and shared decision-making process.

Data Availability

The deidentified data set may be made available upon written request to the corresponding author. Access is conditional upon approval by the CCDHB Clinical Audit and Research Committee and the CCDHB Research Advisory Group Māori.

Conflicts of Interest

None.

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