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Original Article

Is there a limited value of cytoreductive surgery in elderly patients with malignant gliomas?

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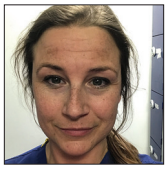

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ABSTRACT

Background: Glioblastoma (GB) is well known for being the most aggressive primary cerebral malignancy. The peak incidence is at 60–70 years of age, with over half of patients aged over 65 years at diagnosis.

Methods: Patients with a confirmed histological diagnosis of GB between January 2009 and June 2016 at a single center were retrospectively identified. The inclusion criteria for the study were age over 65 years at diagnosis, and surgical management with either a burr hole biopsy or craniotomy.

Results: A total of $n = 289$ patients underwent surgery for GB, with a median age at diagnosis of 71 years, and of whom 64% were male. Craniotomies were performed in 71%, with burr hole biopsies performed in the remainder (29%). Patient survival differed significantly with treatment modality ($P < 0.001$), ranging from a median of 382 days in those treated with a combination of craniotomy, radiotherapy (RT), and temozolomide (TZM), to 43 days in those only receiving a burr hole biopsy with no further treatment. On multivariable analysis, treatment with RT + TZM was significantly independently associated with longer patient survival ($P < 0.001$). Craniotomy was associated with a significant improvement in performance status, compared to burr hole biopsy ($P = 0.006$). For the subgroup of patients receiving TZM, those with a methylated O^6-methylguanine-DNA-methyltransferase (MGMT) status had significantly longer overall survival than those with unmethylated MGMT (median: 407 vs. 341 days, $P = 0.039$).

Conclusion: Our retrospective data demonstrate that the elderly population with GB benefit from aggressive chemo-RT, regardless of surgical intervention.

Keywords: Chemotherapy, Craniotomy, Elderly, Glioblastoma, Radiotherapy

INTRODUCTION

With an increase of the worldwide population over the age of 65 from 8.5% (617 million) in 2016 to a projected 25.5% (1.6 billion) in 2050,[8] there is a need to adapt medical management to a greater extent for elderly patients in the future. Glioblastoma (GB) is well known for being the most aggressive primary cerebral malignancy. The peak incidence is at 60–70 years of age, with more than half of patients being older than 65 years when they are diagnosed.[10] The pivotal trial by Stupp *et al.* established 6 weeks of radiotherapy (RT; 60Gy in 30 fractions) plus concurrent chemotherapy with Temozolomide (TZM), followed by 6 months of adjuvant TZM as the standard of care for patients with GB.[34] However, patients over 70 years old were excluded from

this study. A shorter course RT schedule over 3 weeks has been shown to be similar in efficacy to 6 weeks of RT alone in patients over 65 years of age.[25] A further randomized study by Perry *et al*.[23] confirmed that adding concurrent TZM followed by 12 months of adjuvant TZM to this schedule improved overall survival in patients over the age of 65 years (median: 9.3 vs. 7.6 months; hazard ratio [HR]: 0.67; 95% confidence interval [CI]: 0.56–0.80; $P < 0.001$). Patients with methylated O^6-methylguanine-DNA-methyltransferase (MGMT) tumors benefited the most from the addition of TZM to RT, where the median overall survival increased from 7.7 to 13.5 months ($P < 0.001$). A Cochrane meta-analysis has also shown evidence that elderly patients with a GB diagnosis, who are self-caring and treated with chemotherapy and RT have a prolonged survival, compared to RT alone.[11]

There is consensus in the literature that several factors in addition to age play a role in outcomes and survival for elderly patients. Compared to younger patient groups, co-morbidities and performance status (PS) have greater impact on the individual treatment decision in elderly patients,[16] with the PS being the stronger determining factor.[12] Brodbelt *et al*.[4] looked at the English National Cancer Registration Service database for GBs between January 2007 and December 2011, and concluded that the overall outcomes for patients with GB remain poor, but that aggressive treatment is associated with extended survival in every age group. Their data also highlighted that the proportion of patients treated with combined surgery and chemo-RT varied across the geographical regions of the UK. Furthermore, Roth *et al*.[26] suggested that the MGMT status in the elderly, despite overall poor prognosis, can help guide treatment decisions.

Since the publication of data by Perry *et al*.,[23] there is less debate regarding the management of elderly patients with good PS. However, real-world data to demonstrate whether these results can be replicated outside a clinical trial are currently lacking, and uncertainties remain with regard to the optimal extent of surgery, management of reduced PS and the impact of MGMT unmethylated patients. The aim of this study was to explore these issues through evaluation of a large academic hospital practice.

MATERIALS AND METHODS

Patient population

Patients were identified from a local oncology database at our unit in Birmingham, UK. This database contains patients from a single catchment population in and around Birmingham, UK. The patients in this study were selected based on multidisciplinary decisions for surgical intervention, whether this was a simple biopsy for histopathological confirmation of GB to then facilitate an appropriate neuro-oncology management, or a more aggressive surgical debulking. In the UK, oncology treatment cannot be commenced without a biopsy-confirmed diagnosis. As such, those patients where a biopsy was the only surgical management were deemed to be managed conservatively. Inclusion criteria for the study comprised: confirmed histopathology diagnosis of GB, age 65 years or older, and surgical management, which was classified as either a burr hole biopsy or a craniotomy.

A retrospective review of all electronic patient notes was performed, and information collected included diagnosis, MGMT data, PS, oncological management, follow-up, and survival. No patients were treated without histological verification of GB, and all tissue was reviewed by a neurohistopathologist. There has not been a re-review of the tissue following the 2016 glioma classification. Routine MGMT analysis did not start in our unit until 2013 and therefore the data were missing for a number of patients. The type of surgery performed was determined from the operation notes and also by reviewing the postoperative imaging, where available. PS was measured prospectively according to ECOG/WHO PS classification[1,22] and was assessed in clinic when seen for pre- and post-operative assessment by a neurosurgeon and/or oncologist.

Statistical methods

Initially, patient demographics were compared between the groups of surgical and oncological management using Fisher's exact tests for nominal factors and Mann–Whitney U or Kruskal–Wallis tests for ordinal and continuous factors with two, or more than two categories, respectively. Patient survival from diagnosis was then assessed using Kaplan–Meier curves, with HRs produced using univariable Cox regression models. To test for a potential interaction between surgical and oncology management, a Cox regression model was produced with these two factors as covariates, as well as an interaction term. A multivariable Cox regression model was then produced, to identify factors that were independently associated with patient survival.

Analyses were also performed to identify factors associated with the change in PS between the pre- and post-operative periods. The change in status between these periods was divided into three categories: *improved, no change,* and *worsened*. A range of factors was then compared across these categories using Kendall's tau or Kruskal–Wallis tests, for ordinal and nominal factors, respectively. A multivariable analysis was then performed using a binary logistic regression model, to identify independent predictors of an improved (vs. unchanged or worsened) PS postoperatively.

Analyses were then performed for the subgroup of patients for whom the MGMT status was recorded. Comparisons

between those with methylated and unmethylated tumors were performed using Mann–Whitney U or Fisher's exact tests, as applicable. Kaplan–Meier curves and univariable Cox regression analyses were performed separately for the subgroups that did and did not receive chemotherapy.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $p<0.05$ deemed to be indicative of statistical significance throughout.

Ethics approval

This study was registered locally as an audit (CARMS reference number: 17875). Since it utilized pseudonymized data that were retrospectively extracted, formal ethics approval was not sought. This is in accordance with local research policies protocol and the Health Research Authority, UK.

RESULTS

Demographics

A total of n = 289 patients were identified, with a median age at diagnosis of GB of 71 years (interquartile range [IQR]: 68–75), and of whom the majority (64%) were male. Further patient demographics of the cohort are reported in Table 1.

Table 1: Patient demographics.

	n	Statistic
Age at Diagnosis (Years)	289	71 (68–75)
Gender (% Male)	289	186 (64%)
Performance Status (PreOp)	263	
0		40 (15%)
1		131 (50%)
2		55 (21%)
3		28 (11%)
4		9 (3%)
Surgical Management	289	
Biopsy		84 (29%)
Craniotomy		205 (71%)
Performance Status (PostOp)	266	
0		37 (14%)
1		88 (33%)
2		70 (26%)
3		50 (19%)
4		19 (7%)
5		2 (1%)
Oncology Management	289	
None		110 (38%)
RT		92 (32%)
RT+TZM		87 (30%)

Data are reported as *n* (%), or median (interquartile range), as appropriate. Pre/PostOp: Pre-/Postoperative, RT: Radiotherapy, TZM: Temozolomide

Surgical management

The majority of patients were managed with a craniotomy (71%, n = 205), with the remainder (29%, n = 84) having biopsies performed. In the craniotomy group, n = 165 patients had a postoperative scan from which the extent of resection (EOR) could be assessed; of these 70% (116/165) had >80% of the tumor volume resected. Surgical management was found to differ significantly by age at diagnosis, with patients undergoing craniotomies being younger than those treated with biopsies (median: 71 vs. 73 years, P = 0.004). No significant differences in gender distribution (P = 0.685) or preoperative PS (P = 0.115) were detected between the biopsy and craniotomy groups [Table 2]. However, a significant difference in the choice of oncology management was detected (P < 0.001), with patients treated with biopsies being less likely to receive RT and/or TZM than the craniotomy group (46% vs. 68%).

Oncology management

Oncology management was by RT alone in 32% (n = 92) and a combination of RT and TZM (RT+TZM) in 30% (n = 87), with the remainder receiving no oncological treatment (38%, n = 110). Patient age differed significantly between these groups (P < 0.001) [Table 2], with those receiving a RT + TZM being the youngest, at a median of 69 years, compared to 72 years in the other two groups. No significant difference was detected in gender distribution between the groups (P = 0.209). However, a significant difference in preoperative PS scores was observed (P < 0.001), with 88% of patients receiving RT + TZM having scores of 0 or 1, compared to 55% of those in the RT group and 53% of those receiving no oncology management.

Survival

The median survival from diagnosis for the cohort as a whole was 148 days (95% CI: 128–168), and associations between factors and patient survival are reported in Table 3. On univariable analysis, patients managed with a craniotomy, rather than biopsy, had significantly longer survival, with medians of 178 versus 93 days (P < 0.001), [Figure 1a]. Survival also differed significantly by the type of oncology management (P < 0.001), being longest in those receiving RT + TZM, and shortest in those receiving no oncology management (median: 380 vs. 68 days), [Figure 1b]. A Cox regression model containing both surgical and oncology management as factors, as well as the interaction between them, found the interaction term to be non-significant (P = 0.146). This implies that the relative differences in survival between the oncology management groups are similar, regardless of whether a patient had a biopsy or a craniotomy, which can be seen graphically in Figure 2. When combining the groups of surgical and oncological

Table 2: Patient demographics by type of management.

	Surgical Management			Oncology Management			
	Biopsy	**Craniotomy**	***P*-value**	**None**	**RT**	**RT+TZM**	***P*-value**
Age at Diagnosis (Years)	73 (69–77)	71 (68–74)	**0.004**	72 (68–76)	72 (69–77)	69 (67–72)	**<0.001**
Gender (% Male)	56 (67%)	130 (63%)	0.685	65 (59%)	59 (64%)	62 (71%)	0.209
Performance Status (PreOp)*			0.115*				**<0.001***
0	11 (15%)	29 (15%)		11 (12%)	8 (9%)	21 (25%)	
1	31 (42%)	100 (53%)		38 (41%)	39 (45%)	54 (64%)	
2	16 (22%)	39 (21%)		22 (24%)	25 (29%)	8 (9%)	
3	14 (19%)	14 (7%)		14 (15%)	13 (15%)	1 (1%)	
4	2 (3%)	7 (4%)		7 (8%)	1 (1%)	1 (1%)	
Oncology Management			**<0.001**				
None	45 (54%)	65 (32%)		-	-	-	-
RT	30 (36%)	62 (30%)		-	-	-	-
RT+TZM	9 (11%)	78 (38%)		-	-	-	-

Data are reported as *n* (%), with *P*-values from Fisher's exact tests, or as median (interquartile range), with *P* values from Mann–Whitney U or Kruskal–Wallis tests, as applicable, unless stated otherwise. **P*-values are from Mann–Whitney U/Kruskal–Wallis tests, as the factor is ordinal, and only *n* = 263 cases were included in the analysis due to missing data. Bold *P*-values are significant at $P<0.05$. Pre-/PostOp: Pre-/Postoperative, RT: Radiotherapy, TZM: Temozolomide

Table 3: Factors associated with patient survival.

	Median (95% CI) Survival (Days)	**Hazard Ratio (95% CI)**	***P*-value**
Surgical Management			**<0.001**
Biopsy	93 (68–118)	-	-
Craniotomy	178 (145–210)	0.49 (0.37–0.64)	**<0.001**
Oncology Management			**<0.001**
None	68 (44–92)	-	-
RT	145 (118–172)	0.45 (0.34–0.60)	**<0.001**
RT+TZM	380 (330–429)	0.12 (0.08–0.17)	**<0.001**
Surgical+Oncology Management			**<0.001**
Biopsy Only	43 (34–52)	-	-
Craniotomy Only	87 (67–107)	0.47 (0.32–0.70)	**<0.001**
Biopsy and RT	110 (87–133)	0.33 (0.20–0.53)	**<0.001**
Craniotomy and RT	164 (141–187)	0.25 (0.16–0.37)	**<0.001**
Biopsy and RT+TZM	363 (322–404)	0.07 (0.03–0.16)	**<0.001**
Craniotomy and RT+TZM	382 (322–442)	0.07 (0.04–0.10)	**<0.001**
Age at Diagnosis (Years)			**<0.001**
<70	201 (140–262)	-	-
70–74	137 (113–161)	1.29 (0.97–1.70)	0.082
75+	126 (93–159)	1.95 (1.44–2.65)	**<0.001**
Gender			0.860
Male	154 (121–187)	-	-
Female	134 (101–167)	1.02 (0.80–1.31)	0.860
Performance Status (PreOp)			**<0.001**
0	236 (134–338)	-	-
1	178 (136–220)	1.16 (0.81–1.68)	0.420
2	110 (67–153)	1.70 (1.11–2.60)	**0.014**
3–4	104 (73–135)	2.29 (1.44–3.65)	**<0.001**

Median survival times are Kaplan–Meier estimates, and hazard ratios and *P*-values are from univariable Cox regression models. Bold *P*-values are significant at $P<0.05$. CI: confidence interval, PreOp: Preoperative, RT: Radiotherapy, TZM: Temozolomide

management, survival was found to be shortest in those treated with biopsy only, at a median of 43 days, and longest in those treated with a combination of craniotomy and RT + TZM, at a median of 382 days.

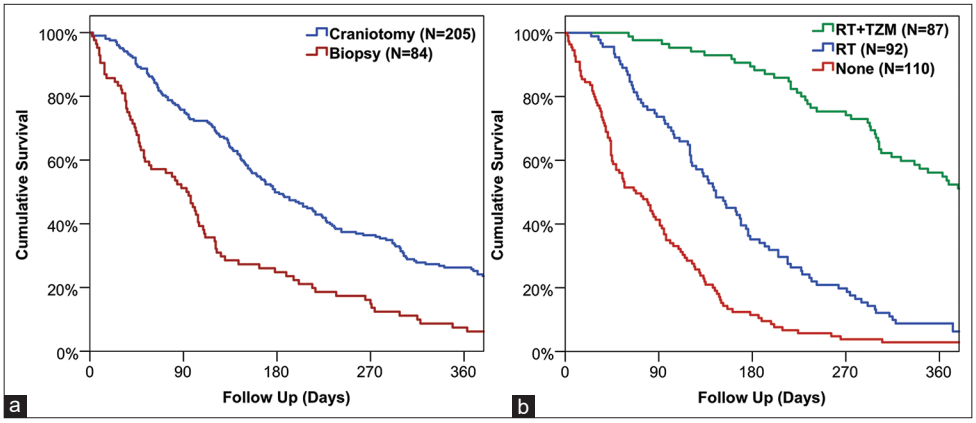

Figure 1: Kaplan–Meier curves of patient survival from diagnosis by (a) surgical and (b) oncology management. The X-axis is truncated at one year to more clearly display the difference between the groups. RT: Radiotherapy, TZM: Temozolomide.

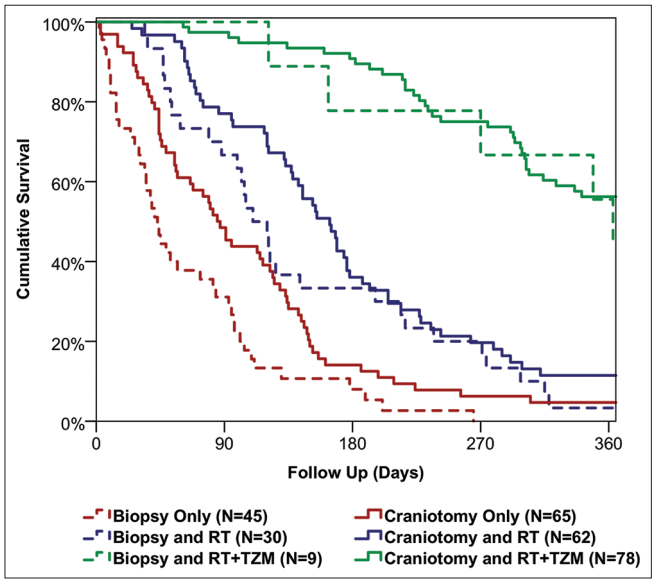

Figure 2: Kaplan–Meier curve of patient survival from diagnosis by treatment group. The X-axis is truncated at 1 year to more clearly display the difference between the groups. RT: Radiotherapy, TZM: Temozolomide.

Of the other factors considered, survival was found to decline significantly with patient age at diagnosis ($P < 0.001$), from a median of 201 days in those aged <70 years to 126 days in those aged 75+ years. In addition, survival declined significantly with the PS score ($P < 0.001$), from a median of 236 days in those with a preoperative score of 0 to 104 days in those scoring 3–4. Since age had previously been found to be significantly associated with both surgical and oncology management, and PS score was associated with the latter, a multivariable analysis was then performed, to account for these potentially confounding factors [Table 4]. This found that, after adjusting for these factors, the oncology management was the strongest predictor of patient outcome ($P < 0.001$). The surgical management did not reach significance in this analysis ($P = 0.052$), although it was patients receiving craniotomies that had a tendency toward improved survival.

Table 4: Multivariable analysis of patient survival.

	Hazard Ratio (95% CI)	*P*-value
Surgical Management		0.052
Biopsy	-	-
Craniotomy	0.75 (0.56–1.00)	0.052
Oncology Management		**<0.001**
None	-	-
RT	0.43 (0.31–0.59)	**<0.001**
RT+TZM	0.12 (0.09–0.18)	**<0.001**
Age at Diagnosis (Years)		0.211
<70	-	-
70–74	1.20 (0.88–1.64)	0.251
75+	1.36 (0.96–1.93)	0.083
Gender		0.567
Male	-	-
Female	1.08 (0.83–1.42)	0.567
Performance Status (PreOp)		0.647
0	-	-
1	1.02 (0.70–1.48)	0.928
2	1.14 (0.74–1.77)	0.552
3–4	1.28 (0.79–2.07)	0.317

Results are from a multivariable Cox regression model, which was based on $n = 249$, after excluding cases with missing values. Bold *P*-values are significant at $P<0.05$. CI: Confidence interval, PreOp: Preoperative, RT: Radiotherapy, TZM: Temozolomide

PS

In the preoperative period, PS was recorded in $n = 263$ patients, of whom 15% ($n = 40$) had a PS of 0, with the most common status being 1 (50%, $n = 131$).

A total of $n = 262$ patients had a PS recorded both pre-and post-operatively. Of these, the PS was unchanged in the majority of patients (57%, $n = 149$), with improvements (i.e., reductions) in 11% ($n = 28$), and worsening (i.e., increases) in 32% ($n = 85$).

On univariable analysis [Table 5], the pre- to post-operative changes in PS were not found to differ significantly by surgical management ($P = 0.166$), age ($P = 0.289$) or gender ($P = 0.197$). A significant association with the preoperative PS was detected ($P < 0.001$), where patients with worse PS preoperatively were more likely to see an improvement postoperatively. In addition, a significant association with oncology management was detected ($P < 0.001$), with those receiving RT + TZM being the most likely to have a postoperative improvement in PS. However, since the oncology management would have commenced after the postoperative PS was measured, this association could not reflect a causal effect. Instead, it is likely that the oncology management was acting as a surrogate marker for the fitness of the patient, as shown by the previously identified correlation with the preoperative PS.

A multivariable analysis was then performed, to identify independent predictors of improvements in PS [Table 6]. Oncology management was not included in this model for the reasons described previously. The analysis found a higher preoperative PS score to be associated with a significantly greater likelihood of improvement in PS ($P = 0.006$). After accounting for this factor, a significant difference between the approaches to surgical management was detected, with those undergoing craniotomy being more likely to see an improvement in the PS than those undergoing biopsies ($P = 0.006$). The associations between these two factors and the changes in PS are visualized in Figure 3. In patients undergoing craniotomy, 11% (11/100), 21% (8/39), and 33% (7/21) of those with a preoperative PS of 1, 2, and 3, respectively, saw a postoperative improvement in PS. This compared to only 3% (1/31), 0% (0/15), and 6% (1/16), respectively, in patients treated with a biopsy.

MGMT status

The MGMT status was only recorded in 106 patients (37%), of whom 52 (49%) had methylated tumors and 54 (51%) were unmethylated. Comparisons between these groups found no significant differences in demographic or treatment-related factors [Table 7]. In those patients that received RT+TZM ($n = 46$), patient survival was found to differ significantly by MGMT status, with median survival of 341 days in unmethylated tumors, compared to 407 days in those that were methylated (HR: 2.19, 95% CI: 1.04–4.60, $P = 0.039$), [Figure 4]. However, for those patients received either no oncology management or RT only ($n = 60$), survival was not found to differ significantly by MGMT status (median: 97 vs. 95 days, HR: 1.01, 95% CI: 0.60–1.72, $P = 0.964$).

Table 5: Factors associated with changes in performance status.

	Change in Performance Status (Pre- to PostOp)			*P*-value
	Improved	**No Change**	**Worsened**	
Surgical Management				0.166
Biopsy	2 (3%)	46 (63%)	25 (34%)	
Craniotomy	26 (14%)	103 (54%)	60 (32%)	
Oncology Management				**<0.001***
None	2 (2%)	52 (57%)	37 (41%)	
RT	10 (12%)	39 (45%)	37 (43%)	
RT+TZM	16 (19%)	58 (68%)	11 (13%)	
Age at Diagnosis (Years)				0.289
<70	8 (9%)	59 (64%)	25 (27%)	
70–74	11 (11%)	55 (57%)	31 (32%)	
75+	9 (12%)	35 (48%)	29 (40%)	
Gender				0.197
Male	11 (12%)	43 (48%)	36 (40%)	
Female	17 (10%)	106 (62%)	49 (28%)	
Performance Status (PreOp)				**<0.001**
0	0 (0%)	23 (58%)	17 (43%)	
1	12 (9%)	71 (54%)	48 (37%)	
2	8 (15%)	30 (56%)	16 (30%)	
3–4	8 (22%)	25 (68%)	4 (11%)	

Analyses are based on the $n = 262$ cases with a performance status recorded both pre- and post-operatively. *P*-values are from Kendall's tau, unless stated otherwise. Bold *P*-values are significant at $P<0.05$. **P*-value from a Kruskal–Wallis test, as the factor is nominal. Pre-/PostOp: Pre-/Post-operative, RT: Radiotherapy, TZM: Temozolomide

DISCUSSION

The current standard of care for GB, the Stupp protocol, includes maximal resection plus adjuvant TZM and RT, resulting in a mean survival of approximately 14 months.[33,34] Several studies have been published looking only at the "elderly" with a GB diagnosis. The Nordic trial[18] found standard RT to be associated with poor outcomes, especially in patients older than 70 years, and concluded that both TZM and hypofractionated RT should be considered as the primary standard treatment options in elderly patients with GB. Surgical resection has been shown to be associated with improved survival, both in the present study, and in the existing literature.[27,31] However, while it is recognized that a craniotomy and debulking of a GB is preferable to a simple biopsy, the optimal EOR is debated.[7,13,15,17,20,28] Gross total resection (GTR) has been shown by multiple retrospective studies and large meta-analyses to improve overall survival and progression-free survival.[3,5,26] Marko *et al.* have suggested a personalized survival model to help in accurate survival prediction, and they also support a maximum-safe-resection approach.[19] GTR needs to be balanced with neurologic compromise,[9] but finding the optimal tumor removal volume can be difficult. Studies have suggested that there may be a non-linear relationship between the EOR and survival, such that above a critical threshold (such as 78%), incomplete resections can have a similar benefit to a GTR.[14,21,23,24,25] Pessina *et al.* also concluded that patients suitable for surgical resection had significantly better outcome.[24] In the present data, the majority of patients undergoing craniotomy and for whom postoperative scans were available, received a resection of >80% of the tumor volume. However, postoperative scans were not available for all patients and, where they were, these were not routinely performed within 48 h. Some scans were also performed without contrast due to patient factors, making it difficult to accurately quantify the extent of the resection. As such, analysis of the impact of EOR on outcomes was outside the scope of the present study.

In our study, overall survival in elderly patients with GB was found to vary dramatically with the extent of treatment, from a median of 382 days in those receiving a craniotomy followed by combined RT and TZM, to just 43 days in those treated with biopsies and no further oncological management.

Table 6: Multivariable analysis of improvement in performance status.

	Odds Ratio (95% CI)	*P*-value
Surgical Management		**0.006**
Biopsy	-	-
Craniotomy	8.15 (1.80–37.77)	**0.006**
Age at Diagnosis (Years)		0.384
<70	-	-
70–74	1.33 (0.49–3.62)	0.577
75+	2.10 (0.73–6.10)	0.171
Gender		0.886
Male	-	-
Female	1.06 (0.46–2.48)	0.886
Performance Status (PreOp)		**0.006**
0–1	-	-
2	2.34 (0.88–6.23)	0.090
3–4	5.47 (1.91–15.72)	**0.002**

Results are from a multivariable binary logistic regression model, with the dependent variable specifying whether or not the performance status improved from the pre- to post-operative periods. Oncology management was not included in the model, as this begins after the postoperative performance status has been measured. The preoperative performance status groups 0 and 1 were combined, as there were no outcomes in the former, making odds ratios incalculable. The model was based on the $n = 262$ with a performance status recorded both pre- and post-operatively. Bold *P*-values are significant at $P<0.05$. CI: Confidence interval, PreOp: Pre-operative

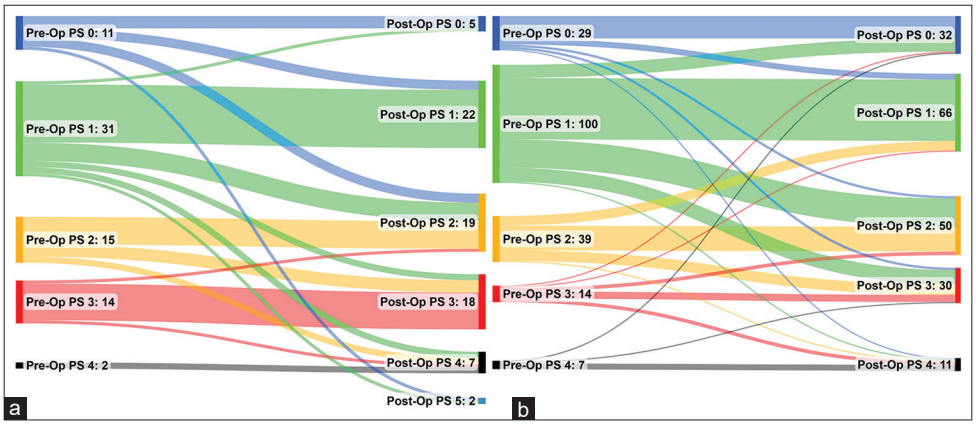

Figure 3: Sankey diagram of the pre- to post-operative changes in performance status after (a) biopsy and (b) craniotomy. Patients with missing data for either the pre- or post-operative assessment are excluded, hence the plots are based on $n = 73$ for biopsy and $n = 189$ for craniotomy. Pre-/PostOp: Pre-/PostOperative, PS: performance status.

Table 7: Patient demographics by MGMT status.

	MGMT Status		
	Methylated	**Unmethylated**	***P*-value**
Age at Diagnosis (Years)	72 (67–6)	70 (68–73)	0.383
Gender (% Male)	33 (63%)	42 (78%)	0.136
Performance Status (PreOp)*			0.504*
0	12 (25%)	14 (29%)	
1	25 (52%)	27 (55%)	
2	10 (21%)	6 (12%)	
3	0 (0%)	1 (2%)	
4	1 (2%)	1 (2%)	
Surgical Management			0.823
Biopsy	12 (23%)	14 (26%)	
Craniotomy	40 (77%)	40 (74%)	
Oncology Management			0.100
None	12 (23%)	20 (37%)	
RT	12 (23%)	16 (30%)	
RT+TZM	28 (54%)	18 (33%)	

Data are reported as *n* (%), with *P*-values from Fisher's exact tests, or as median (interquartile range), with *P*-values from Mann–Whitney U tests, as applicable, unless stated otherwise. **P*-values are from Mann–Whitney U tests, as the factor is ordinal, and only *n* = 97 cases were included in the analysis, due to missing data. Bold *P*-values are significant at $P<0.05$. PreOp: Preoperative, RT: Radiotherapy, TZM: Temozolomide, MGMT: O^6-methylguanine-DNA-methyltransferase

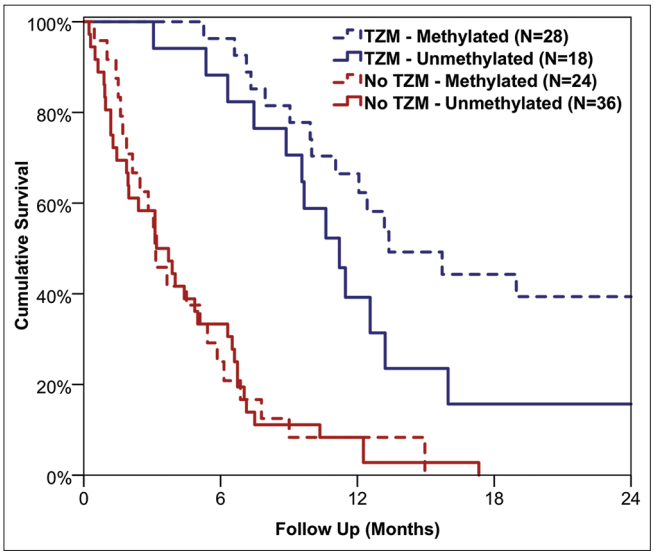

Figure 4: Kaplan–Meier curve of patient survival from diagnosis by treatment group and MGMT status. The X-axis is truncated at two years to more clearly display the difference between the groups. MGMT: O6-methylguanine-DNA-methyltransferase, TZM: Temozolomide.

However, the major issue with comparing outcomes between treatments in a retrospective or non-randomized study design is the confounding effect of case selection. Patients treated with the most aggressive surgical and neuro-oncology management were found to be significantly younger than those receiving more conservative treatment; specifically, younger patients were more likely to be treated with craniotomy (vs. biopsy) and to receive combined TZM and RT. The previous studies have also highlighted that elderly populations are less likely to receive oncology treatment in general, which could be reflection of older patients being less amenable to aggressive interventions, due to lower physiological resilience and poorer preoperative PS.[28,29] The impact of PS was also observed in the present study, with patients scoring 0–1 preoperatively being considerably more likely to receive combined TZM and RT, although preoperative PS did not appear to significantly influence the surgical approach.

In an attempt to adjust for the confounding effects of age and PS, as well as to isolate the effects of surgical and oncology management, a multivariable analysis was performed. This found the approach to oncology management to be independently associated with overall survival, with combined RT and TZM leading to the best survival outcomes. After adjusting for effect of oncological management, the benefit of craniotomy (vs. biopsy) was found to be relatively small in comparison, and did not reach statistical significance in the final model. In addition, neither patient age nor preoperative PS was found to be significant independent predictors of overall survival in this model, implying that it is the largely the extent of oncological treatment, rather than surgical treatment, age or PS, that moderates survival for elderly patients with GB in our study.

While craniotomy was not found to be a significant independent predictor of overall survival, patients undergoing craniotomy were significantly more likely to see a postoperative improvement in PS, compared to those treated with biopsies. This was particularly pronounced in those with the poorest preoperative PS (i.e., scoring 3–4), where 33% of those receiving a craniotomy saw a postoperative improvement in PS, compared to 6% of those treated with biopsies. As such, while the direct benefit of craniotomy on patient survival was modest, the postcraniotomy improvement in PS may have allowed some patients who were previously unfit for aggressive oncological management to receive RT and TZM, indirectly improving their prognosis. The argument here would suggest that even patients with a poor PS should be considered for a craniotomy, provided the tumor is a suitable operative target. Other complementary treatments, such as corticosteroids, should also be considered and optimized, to give patients the best possible chance of tolerating aggressive surgical and oncological management.

The tradition of cytoreductive surgery is to some extent becoming less central to the management of GB with the identification of tumor biomarkers. MGMT methylation

status is one of many such biomarkers, which is used to optimize treatment, with an aim to maximize patient survival. Unmethylated MGMT tumors are unlikely to respond to TZM, which was also observed in our study, with TZM offering no significant survival benefit in this subgroup of tumors. As such, there are clear benefits to maximizing the EOR (≥86%) in these unmethylated MGMT tumors.[26,32] On the other hand, methylated MGMT tumors are likely to respond to treatment with TZM; hence, optimizing oncological management should be the prioritized in these patients, with extensive EOR playing a lesser prognostic role.[32] Molecular diagnostics are now part of the WHO classification for CNS tumors since 2016. These are important factors to take into consideration in the management of all patients with a GB diagnosis, particularly the elderly, as they can help to identify patients with different molecular status and optimize medical management, potentially leading to increased survival, reduced toxicity and improved quality of life.[6]

The "Glioma Cancer research in the 100,000 genome project" is a project that will be looking to find important genetic mutations that can help improve care and tailor treatment for patients diagnosed with GB. The project has started recruiting in the UK, and all age groups are eligible for enrollment. It will be interesting to see the results and what benefits it can bring to the elderly in particular with a GB diagnosis.[2]

To summarize, elderly patients will have a poorer PS compared to younger patients and, consequently, are less likely to receive aggressive interventions in the form of surgery, RT and chemotherapy.[28] If given the opportunity, this elderly cohort should tolerate the Stupp protocol well, and generally had similar favorable outcomes compared to those treated on EORTC 22,981 trial.[3] It would follow that craniotomy followed by TZM and RT, a good PS and methylated MGMT status would predispose to better overall survival. The growing evidence in the literature that aggressive treatment of the elderly is effective in prolonging overall survival[30,35] makes it important to include the elderly population in future trials and research around this aggressive tumor.

Limitations of this study

The primary limitation of the study was the potential for section bias and confounding, in light of the retrospective design. The surgical and oncological management approaches differed significantly by age and PS, which will have acted as confounding factors in the analysis. Multivariable analyses were performed, in an attempt to adjust for the effects of these factors, and isolate the independent effects of treatment. However, it is likely that some degree of residual confounding will be present, both due to confounders that were not considered and imperfect model fit, meaning that significant relationships can only be inferred to be indicative of associations with outcomes, rather than causal effects. In addition, the data were from a single center, and so may not be generalizable to other centers, particularly those with different patient demographics and treatment protocols.

CONCLUSION

Our retrospective data demonstrate that the elderly population with GB can derive significant benefit from aggressive oncology treatment with combined RT and TZM, regardless of surgical intervention. Whilst combining this with craniotomy resulted in the longest survival, the direct benefit over a simple biopsy was modest. However, craniotomy did lead to improved PS, which could subsequently increase the likelihood of a patient being deemed eligible for more aggressive oncological treatment. Therefore, every attempt should be made to offer these patients an optimal treatment, with all options taken into consideration. This degree of management requires close cooperation among neurosurgeons, anesthetists, neuro-oncologists, and neuropathologists to carefully select patients who are fit enough to benefit from this demanding treatment.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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