Cancer Causes & Control (2021) 32:327–336
https://doi.org/10.1007/s10552-020-01388-9

ORIGINAL PAPER

Body mass index as an independent prognostic factor in glioblastoma

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Received: 11 August 2020 / Accepted: 22 December 2020 / Published online: 15 January 2021

Abstract

Purpose Glioblastoma prognosis remains dismal despite gross total removal (GTR) followed by chemoradiotherapy. Other known prognostic factors include functional status, age and IDH mutation status. However, to improve patient outcome, a search for other features with impact on survival is needed. We aimed to analyse the impact of body mass index (BMI) on overall survival (OS) and progression-free survival (PFS) of surgically resected primary glioblastoma and evaluate if BMI constitutes an independent prognostic factor.

Methods We analysed all adult glioblastoma patients who underwent surgery and chemoradiotherapy between 2011 and 2017 at our institution. Overall survival was the study—primary endpoint, and progression-free survival—the secondary endpoint. We assayed age, gender, histology, extent of resection, IDH, functional and smoking status, cardiovascular risk factors, BMI, OS and PFS. Univariate analysis was conducted followed by multivariate analysis to establish independent prognostic factors. In accordance with the World Health Organization (WHO) BMI stratification, survival curves were obtained for normal-weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese ($\geq$ 30 kg/m^2) patient subgroups in addition to the non-obese (18.5–29.9 kg/m^2) population.

Results 193 patients were evaluated, with a median follow-up time of 17.3 months. Median OS was 21.3 months in obese patients vs 16.2 months in the non-obese ($p = 0.017$) and 16 months in the normal weight ($p = 0.007$). Higher median OS was also observed in patients under 60 and those in which GTR was obtained. Median PFS in obese individuals was 9 months in comparison to 6 months in the normal-weight subgroup ($p = 0.04$) and 7 months in the non-obese ($p = 0.050$). Multivariate analysis identified age < 60 ($p = 0.044$), GTR ($p = 0.004$) and BMI $\geq$ 30 ($p = 0.009$) as independent prognostic factors for increased overall survival.

Conclusion Higher BMI was associated with longer OS and PFS. Prospective studies are needed to validate these findings.

Keywords Glioblastoma · Body mass index · Obese · Overall survival · Progression-free survival

Abbreviations

GBM	Glioblastoma
RT	Radiotherapy
TMZ	Temozolomide
TTFields	Tumour-treating fields
GTR	Gross total removal
IDH	Isocitrate dehydrogenase
CNS	Central nervous system
BMI	Body mass index
EOR	Extent of resection
OS	Overall survival
PFS	Progression-free survival
CHUSJ	Centro Hospitalar Universitário São João
WHO	World Health Organization
MGMT	*O*-6-Methylguanine-DNA methyltransferase
HGG	Higher-grade glioma
RCC	Renal cell cancer
CSS	Cancer-specific survival
FASN	Fatty acid synthase

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Introduction

Glioblastoma (GBM) is the most aggressive primary malignant brain tumour in the adult population. Despite increased survival after the introduction of radiotherapy (RT), temozolomide (TMZ) and more recently tumour-treating fields

(TTFields), to the therapeutic plan, prognosis remains dire with 5-year survival under 5% [1].

Gross total removal (GTR) followed by chemoradiotherapy is associated with better outcomes [2]. Age, functional performance status and isocitrate dehydrogenase (IDH) mutation status are also important prognostic factors [1].

Excess body weight and obesity are known risk factors for the development of various neoplasms, and in the central nervous system (CNS), meningiomas have been linked to higher body weight [3–6]. Hormonal imbalance, chronic inflammation and increased insulin resistance are among the factors associated with increased cancer risk in overweight and obese patients [7, 8]. Furthermore, in some studies, excess body weight had a negative impact on cancer morbidity and mortality [9, 10].

The association between body mass index (BMI) and glioma occurrence is less clear, and no association has thus far been found between higher body weight and glioma risk [11–13].

In addition, there is conflicting evidence regarding BMI impact on higher-grade glioma patients´ survival [14–17].

In 2013, Siegel et al. reported decreased survival of prediagnostic underweight and obese higher-grade glioma subjects [14]. However, BMI was subjectively assayed based on patients' own perceived weight 1–5 years prior to diagnosis, and multivariate analysis was not adjusted for extent of resection (EOR).

In a prospective study published in 2010, Jones and colleagues found no association between body weight and survival rates in 1,259 previously untreated glioblastoma patients diagnosed between 1991 and 2008 [15].

However, due to the study´s timeframe, most patients did not undergo chemoradiotherapy according to the Stupp protocol, which has become the standard of care in glioblastoma treatment [16].

More recently, Potharaju et al. reported increased survival of overweight and obese GBM patients [17].

In this study, we aimed to evaluate the impact of BMI on overall survival (OS) and progression-free survival (PFS) of surgically resected primary glioblastoma and to assess whether BMI constitutes an independent prognostic factor.

Methods

Study design and patient selection

We retrospectively reviewed the clinical files of all adult glioblastoma patients who underwent surgery and adjuvant chemoradiotherapy treatment between 2011 and 2017 at Centro Hospitalar Universitário São João (CHUSJ), Porto, Portugal.

A total of 193 patients with histologically proven GBM were evaluated for clinical progression and outcome through assessment of medical records from Neurosurgery, Oncology and Radiotherapy inpatient and outpatient consultations.

Patients with post-op vascular lesions or systemic infections that precluded chemoradiation, secondary glioblastomas and biopsies were excluded. Additionally, one underweight, two normal-weight and one overweight patient were not included due to aggressive tumour recurrence before initiating or completing the first cycle from the Stupp protocol. We evaluated extent of resection, age, gender, functional status (ECOG), tumour histology, BMI, IDH-status, PFS and OS. Additionally, smoking status and cardiovascular risk factors including hypertension, dyslipidaemia and diabetes mellitus were assayed.

Overall survival was calculated from date of surgery to date of death or when alive to last medical evaluation. Progression-free survival was calculated from date of surgery to date of imaging or clinical recurrence, whatever took place first, or when progression did not occur to last medical consultation.

BMI was obtained from oncology outpatient consultations before the start of chemoradiotherapy.

Body mass index was classified according to World Health Organization (WHO) categories: normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese ($\geq$ 30 kg/m^2).

Besides comparison within WHO BMI subsets, we further compared overall survival and progression-free survival of obese patients with normal-weight plus overweight individuals.

Glioblastoma diagnosis was obtained by histological analysis of surgical specimens by the Department of Pathology at our institution while IDH 1/2 mutation status was confirmed through immunohistochemistry and genotyping.

189 patients had de novo IDH-wild-type glioblastoma while 4 patients had de novo IDH—mutant glioblastoma.

O-6-Methylguanine-DNA methyltransferase (MGMT) gene promoter methylation status was not routinely performed at our institution until 2017, and thus, results were only obtained for four patients.

192 patients were submitted to chemoradiation according to the Stupp protocol while a normal-weight elderly patient with positive MGMT promoter methylation status completed treatment with temozolomide. Second-line therapy after progression was bevacizumab-based in all subjects, and 26 patients had one surgery for tumour recurrence while two patients had two re-operations.

The diagnosis of hypertension, dyslipidaemia and diabetes mellitus had previously been established by the patients´ general practitioners or by previous hospitalizations and was obtained through the patients´ medical records.

Data and statistical analysis

We used IBM SPSS Statistics 26 software.

Overall survival was the study—primary endpoint, and progression-free survival—the secondary endpoint. A p value below 0.05 was considered statistically significant. Differences between groups were evaluated with Chi-square or Mann–Whitney U tests.

We performed univariate analysis of BMI, gender, smoking status, cardiovascular risk factors and known prognostic factors including age, functional status and EOR.

Current smokers and ex-heavy smokers (≥ 1 pack of cigarettes per day in the previous 15 years) were considered as smokers.

For univariate analysis, a post-op residual tumour volume < 2.5 cm^3 and $< 2\%$ on MRI was considered GTR while age-wise patients were divided into two groups: < 60 and ≥ 60 years.

For performance status, patients were divided into two groups: ECOG 0–1 and ECOG 2–4.

We conducted multivariate analysis of OS and PFS through Cox proportional hazards regression for variables with p value < 0.10 on univariate analysis in order to determine independent prognostic factors.

PFS and OS curves were obtained through the Kaplan–Meier method with 95% confidence intervals for the three categories of BMI and the normal plus overweight subgroup.

Results

A total of 193 patients were evaluated, 116 men (60.1%) and 77 women (39.9%), with a median age of 60 years. 32 patients were obese, 102 were overweight, while the remaining 59 had normal weight.

Median overall survival and follow-up time for all 193 patients was 17.3 months while median progression-free survival was 7.5 months.

At the time of last medical follow-up, eight (25%) obese, 13 (12.7%) overweight and two (3.4%) normal-weight patients were alive while two (6.3%) obese and six (5.9%) overweight subjects had not shown signs of imaging or clinical tumour recurrence. In all normal-weight patients, disease progression had occurred.

Patient groups

Table 1 details patients' characteristics by BMI group.

Chi-square and Mann–Whitney U tests were run to rule out discrepancies within groups for age, EOR, performance and smoking status.

Median age was 62 years for obese subjects, 57 years for the non-obese (Mann–Whitney U test $p = 0.234$), 60 years for overweight patients ($p = 0.335$) and 59 years for the normal weight ($p = 0.495$).

Similarly, between the aforementioned groups, no statistical difference was found in ECOG performance status, smoking status and EOR.

Univariate analysis

Table 2 details p values obtained on univariate analysis.

Median overall survival was 21.3 months (CI 16.9–25.7) in subjects with BMI ≥ 30 kg/m^2 and 16.2 months in the non-obese (CI 14–18.3) (p value $= 0.017$).

Median OS was 19.3 months (CI 17–21.6) in those aged < 60 and 14.8 months in patients aged ≥ 60 (CI 13.2–16.4) (p value $= 0.020$).

Patients with GTR had a median OS of 19 months (CI 15.8–22.2) that compared to 14.6 months in subtotal resection (CI 11.1–18) (p value $= 0.001$).

Median OS was 18 months for ECOG 0–1 patients (CI 15.9—20) and 14.6 months in the ECOG 2–4 subgroup (CI 11.5–17.7) (p value $= 0.085$).

Median OS was 18.1 months (CI 15.2–21) and 17 months (CI 15–18.9) for females and males, respectively (p-value $= 0.127$).

Median OS was 15.2 months (CI 10.7–19.7) and 18 months (CI 15.8–20.2) for diabetic and non-diabetic subjects, respectively ($p = 0.099$).

Median progression-free survival was 9 months (CI 7.4–10.6) and 7 months (CI 6.3–7.7) in the obese and the non-obese patient subgroups, respectively ($p = 0.050$).

Patients with GTR had a median PFS of 8 months (CI 7.1–8.8) while those with subtotal resection had a median PFS of 6 months (CI 5–7) ($p = 0.037$).

ECOG, cardiovascular risk factors, smoking status, age and gender had no statistically significant impact on PFS.

Median OS and PFS within groups

Tables 3 and 4 detail OS and PFS within BMI subgroups and within gender.

Figure 1 includes survival curves for age, EOR, OS and PFS according to BMI category.

Median OS was 21.3 months in the obese subgroup (CI 16.9–25.7), 17.2 months (CI 13.5–20.9) in overweight patients ($p = 0.184$) and 16 months (CI 13.9–18) in the normal-weight population ($p = 0.007$).

Median PFS was 9 months in the obese subgroup (CI 7.4–10.6), 7 months (CI 5.8–8.2) in overweight patients ($p = 0.178$) and 6 months (CI 4.9–7) in the normal-weight population ($p = 0.004$).

Table 1 Patient characteristics by BMI category

BMI category	Normal	Overweight	Obese
Total patients ($n=193$)	59 (30.6%)	102 (52.8%)	32 (16.6%)
Males ($n=116$) (60.1%)	36 (61.1%)	69 (67.6%)	11 (34.4%)
Females ($n=77$) (39.9%)	23 (38.9%)	33 (32.4%)	21 (65.6%)
Extent of resection			
Total ($n=111$) (57.5%)	29 (49.1%)	60 (58.8%)	22 (68.8%)
Subtotal ($n=82$) (42.5%)	30 (50.9%)	42 (41.2%)	10 (31.2%)
ECOG performance status			
ECOG 0–1 ($n=156$) (80.8%)	47 (79.7%)	83 (76.1%)	26 (81.2%)
ECOG 2–4 ($n=37$) (19.2%)	12 (20.3%)	19 (23.9%)	6 (18.8%)
Age	Median age = 59 years	Median age = 60 years	Median age = 62 years
< 60 years ($n=98$) (50.7%)	30 (50.9%)	50 (49%)	18 (56.2%)
≥ 60 years ($n=95$) (49.3%)	29 (49.1%)	52 (51%)	14 (43.8%)
IDH status			
Wild type ($n=189$) (98.5%)	58 (98.3%)	100 (98%)	31 (96.9%)
IDH mutated ($n=4$) (1.5%)	1 (1.7%)	2 (2%)	1 (3.1%)
Smoking status			
Smoker ($n=28$) (14.5%)	8 (13.6%)	16 (15.7%)	4 (12.5%)
Non-smoker ($n=165$) (85.5%)	51 (86.4%)	86 (84.3%)	28 (87.5%)
Diabetes mellitus			
Yes ($n=28$) (14.5%)	5 (8.5%)	15 (14.7%)	8 (25%)
No ($n=165$) (85.5%)	54 (91.5%)	87 (85.3%)	24 (75%)
Hypertension			
Yes ($n=81$) (41.9%)	14 (23.7%)	45 (44.1%)	22 (68.8%)
No ($n=112$) (58.1%)	45 (76.3%)	57 (55.9%)	10 (31.2%)
Surgery for recurrence			
0 ($n=165$) (85.5%)	50 (84.7%)	87 (85.3%)	28 (87.5%)
1 ($n=26$) (13.5%)	8 (13.6%)	14 (13.8%)	4 (12.5%)
2 ($n=2$) (1%)	1 (1.7%)	1 (0.9%)	0
Median overall survival	16 months (CI 13.9–18)	17.2 months (CI 13.5–20.9)	21.3 months (CI 16.9–25.7)
Median progression-free survival	6 months (CI 4.9–7)	7 months (CI 5.8–8.1)	9 months (CI 7.4–10.6)

Gender-wise median OS was 21.5 months in male obese patients (CI 16.5–26.5), 16.2 months (CI 13.7–18.7) in the non-obese ($p=0.217$), 17.6 months (CI 12.4–22.8) in the overweight ($p=0.321$) and 15.5 months in normal-weight males (CI 12.2–18.7) ($p=0.109$).

There was no statistically significant difference in median PFS within male BMI subgroups.

Median OS was 21.3 months (CI 11–31.6) in obese females, 16.3 months (CI 12.7–19.9) in the non-obese ($p=0.076$), 15.7 months (CI 9–22.3) in the overweight ($p=0.160$) and 16.3 (CI 12–20.6) months in normal-weight women (p value = 0.073).

Median PFS was 9.5 months in obese females (CI 5–13.9) and 7 months in normal-weight women (CI 5.2–7.7) (p value = 0.017).

Independent prognostic factors

A multivariate analysis on overall survival with cox-regression including univariate p values < 0.1 was conducted and age < 60 (p value = 0.044; HR 0.73), gross total resection (p value = 0.004; HR 0.62) and body mass index ≥ 30 (p value = 0.009; HR 0.56) were identified as independent prognostic factors associated with longer survival.

Multivariate analysis on progression-free survival did not identify either GTR (p value = 0.066; HR 0.76) or BMI ≥ 30 (p value = 0.083; HR 0.7) as statistically significant independent prognostic factors.

Table 2 Kaplan–Meier pairwise comparison of prognostic factors and cox-regression p values for prognostic factors with $p < 0.1$ on univariate analysis

Prognostic factor	Median OS	Median PFS	X^2 square OS	X^2 square PFS	p value OS	p value PFS	Multivariate analysis p-value
EOR total	19 months (CI 15.8–22.2)	8 months (CI 7.1–8.9)	11.443	4.332	0.001	0.037	0.04 (HR 0.62)/0.066 (HR 0.76)
EOR subtotal	14.6 months (CI 11.1–18)	6 months (CI 5–6.9)					
ECOG 0–1	18 months (CI 15.9–20)	8 months (CI 7–9.1)	2.962	0.702	0.085	0.402	0.67 (HR 0.91)/–
ECOG 2–4	14.6 months (CI11.5–17.7)	6 months (CI 5–6.9)					
Age < 60 years	19.3 months (CI 17–21.6)	8 months (CI 7–8.9)	5.390	0.842	0.020	0.359	0.044 (HR 0.73)/–
Age > 60 years	14.8 months (CI 13.2–16.4)	6 months (CI 5.2–6.8)					
Obese	21.3 months (CI 16.9–25.7)	9 months (CI 7.4–10.6)	5.687	3.848	0.017	0.050	0.009 (HR 0.56)/0.083 (HR 0.7)
Non-obese	16.2 months (CI 14–18.3)	7 months (CI 6.3–7.7)					
Obese	21.3 months (CI 16.9–25.7)	9 months (CI 7.4–10.6)	7.395	8.166	0.007	0.004	–
Normal weight	16 months (CI 13.9–18)	6 months (CI 4.9–7)					
Obese	21.3 months (CI 16.9–25.7)	9 months (CI 7.4–10.6)	3.625	1.812	0.057	0.178	–
Overweight	17.2 months (CI 13.5–20.9)	7 months (CI 5.8–8.1)					
Overweight	17.2 months (CI 13.5–20.9)	7 months (CI 5.8–8.1)	1.763	3.657	0.184	0.056	–
Normal weight	16 months (CI 13.9–18)	6 months (CI 4.9–7)					
Smoker	14.7 months (CI 6.9–22.5)	7 months (CI 5.7–8.2)	0.049	0.181	0.825	0.670	–
Non-smoker	17.3 months (CI 15.5–19)	7.5 months (CI 6.4–8.6)					
Diabetic	15.2 months (CI 10.7–19.7)	6 months (CI 5.2–6.8)	2.718	1.332	0.099	0.248	0.137 (HR 0.7)/–
Non-diabetic	18 months (CI 15.8–20.2)	8 months (CI 7–8.9)					
Hypertense	15.5 months (CI 12.9–18.1)	8 months (CI 6.4–9.6)	0.802	0.123	0.370	0.726	–
Non-hypertense	18 months (CI 16–19.9)	7 months (CI 5.7–8.3)					

Discussion

Glioblastoma remains a biological and clinical challenge with dismal long-term survival despite best care with maximal extent of resection and chemoradiotherapy. A reduced number of patients are able to live for many years without signs of disease and a few others maintain long-term disease stability after tumour recurrence.

In order to improve patient outcome, it is of paramount importance to identify subgroups of subjects with increased OS or PFS that share clinical or tumour biological characteristics. Understanding the mechanism behind such phenomenon might lead to better tumour pathogenesis knowledge and help find novel molecular and clinical therapeutic targets.

In a 2018 retrospective series of 392 GBM patients, Potharaju et al. [17] sought to analyse the effect of BMI on overall survival. The overweight and obese patients had statistically significant longer median OS when compared to normal-weight subjects. We report similar results. Statistically significant increased OS and PFS were observed in

Table 3 Statistical comparison between BMI categories regarding overall survival (*p* values in the center squares)

	Normal weight Total: 16 months (CI 13.9–18) Males: 15.5 months (CI 12.2–18.7) Females: 16.3 months (CI 12–20.6)	Overweight Total: 17.2 months (CI 13.5–20.9) Males: 17.6 months (CI 12.4–22.8) Females: 15.7 months (CI 9–22.3)	Obese Total: 21.3 months (CI 16.9—25.7) Males: 21.5 months (CI 16.5—26.5) Females: 21.3 months (CI 11–31.6)	Non-obese Total: 16.2 months (CI 14–18.3) Males: 16.2 months (CI 13.7–18.7) Females: 16.3 months (CI 12.7–19.9)
Normal weight				
Total: 16 months (CI 13.9–18)	–	0.184	0.007	–
Males: 15.5 months (CI 12.2–18.7)		0.201	0.109	
Females: 16.3 months (CI12–20.6)		0.574	0.073	
Overweight				
Total: 17.2 months (CI 13.5–20.9)	0.184	–	0.057	–
Males: 17.6 months (CI 12.4–22.8)	0.201		0.321	
Females: 15.7 months (CI 9–22.3)	0.574		0.160	
Obese				
Total: 21.3 months CI (16.9–25.7)	0.007	0.057	–	0.017
Males: 21.5 months (CI 16.5–26.5)	0.109	0.321		0.217
Females: 21.3 months (CI 11–31.6)	0.073	0.160		0.076
Non-obese				
Total: 16.2 months (CI 14–18.3)	–	–	0.017	–
Males: 16.2 months (CI 13.7–18.7)			0.217	
Females: 16.3 months (CI 12.7–19.9)			0.076	

Table 4 Statistical comparison between BMI categories regarding progression-free survival (*p* values in the center squares)

	Normal weight Total: 6 months (CI 4.9–7) Males: 6 months (CI 5–7) Females: 7 months (CI 5.2–7.7)	Overweight Total: 7 months (CI 5.8–8.1) Males: 7.5 months (CI 6.3–8.6) Females: 6 months (CI 5.7–6.3)	Obese Total: 9 months (CI 7.4–10.6) Males: 9 months (CI 7.4–10.6) Females: 9.5 months (CI 5–13.9)	Non-obese Total: 7 months (CI 6.3–7.7) Males: 7 months (CI 5.6–8.4) Females: 6 months (CI 5–6.9)
Normal weight				
Total: 6 months (CI 4.9–7)	–	0.056	0.004	–
Males: 6 months (CI 5–7)		0.172	0.272	
Females: 7 months (CI 5.2–7.7)		0.231	0.017	
Overweight				
Total: 7 months (CI 5.8–8.1)	0.056	–	0.178	–
Males: 7.5 months (CI 6.3–8.6)	0.172		0.696	
Females: 6 months (CI 5.7–6.3)	0.231		0.399	
Obese				
Total: 9 months (CI 7.4–10.6)	0.004	0.178	–	0.050
Males: 9 months (CI 7.4–10.6)	0.272	0.696		0.524
Females: 9.5 months (CI 5–13.9)	0.017	0.399		0.119
Non-obese				
Total: 7 months (CI 6.3–7.7)	–	–	0.050	–
Males: 7 months (CI 5.6–8.4)			0.524	
Females: 6 months (CI 5–6.9)			0.119	

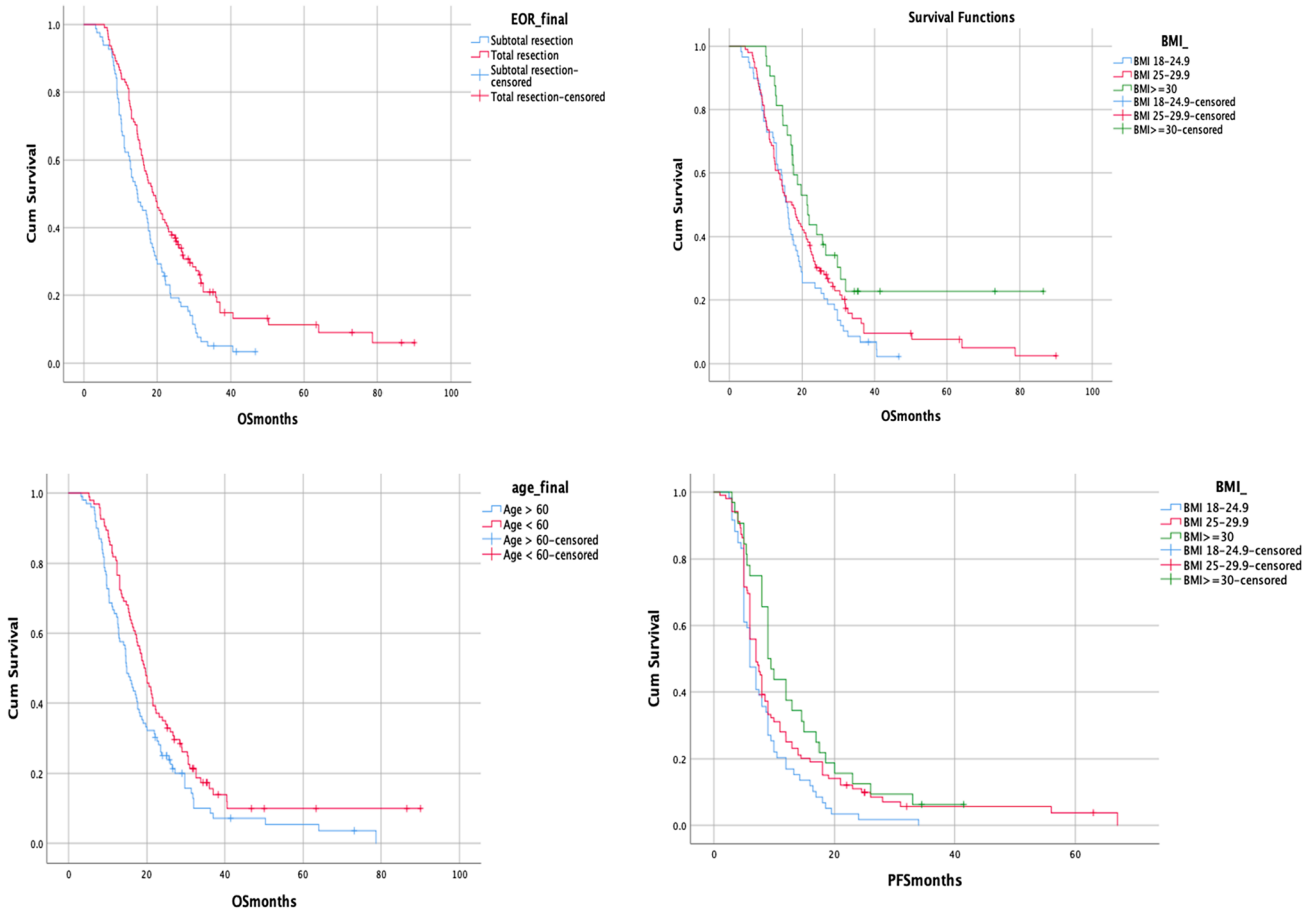

Fig. 1 Overall survival functions for EOR, BMI category and age. On the bottom right, survival curve for PFS according to BMI subset

obese patients in comparison to normal-weight subjects, and increasing BMI was associated with higher OS.

When adjusted for other prognostic factors on multivariate analysis, a BMI ≥ 30 kg/m^2 had a statistically significant positive impact on outcome, similar to gross total resection and younger age.

BMI and cancer link

The term "obesity paradox" has been used to describe the longer cancer survival of overweight and obese patients even though excess body weight is associated with increased cancer risk.

Some authors [18–20] have tried to explain those findings by pinpointing to methodological flaws of previous studies, namely inadequacy of BMI to determine body composition, existence of confounders, detection bias and reverse causation. Park et al. [18] and Lennon and colleagues [19] argue that body mass index is not the ideal measurement of body fat and better predictors of adiposity and body composition should be used before establishing a link between BMI and increased survival. Whilst true, body fat measurement with BMI still remains the clinical benchmark as other methods are at the current time not suitable for clinical practice.

In our study, the obese subgroup had better OS and PFS outcomes, and while body composition might be harder to gauge in the overweight, excess adiposity is almost certain in the obese.

Furthermore, BMI was the clinical marker used to link excess body weight and adiposity to cancer risk in multiple studies [21–23].

Confounders such as smoking status and comorbidities have also been used to try to explain the obesity paradox.

In our study, there was no statistically significant difference between groups in smoking and ECOG performance status and as expected cardiovascular risk factors were more frequent in the overweight and obese subgroups; thus, our overweight and obese patients were unlikely to be healthier than normal-weight individuals. Median age for the obese and overweight subgroups was also higher.

Unsurprisingly, detection bias does not apply to glioblastoma as the natural history of the disease is rapid and as such reverse causation is also less likely to be a factor in

glioblastoma patients as GBM-induced weight loss is less exuberant than other cancers.

At our institution and with few exceptions, glioblastomas are operated within a week of MRI-imaging diagnosis and steroids are usually tapered off post-operatively during a 5–10 day period. Therefore, steroid usage is unlikely to have significantly impacted BMI.

Socioeconomical disparity between groups is also unlikely to explain the difference in OS and PFS as all patients received treatment in a public hospital, where healthcare access is free and universal.

We believe there may be other factors besides heterogeneity within different BMI groups and the lack of a more effective means to establish body composition in standard clinical practice that can justify the longer survival of overweight and obese cancer patients observed in various studies.

Higher BMI and cancer survival

Multiple studies have reported increased survival of overweight and obese subjects relative to under and normal-weight individuals after cancer diagnosis [24, 25].

In their evaluation of BMI and outcome in colorectal cancer, Shahjehan et al. [26] demonstrated that being underweight was a negative predictor of outcome and when all stages of cancer were combined obese and overweight subjects lived longer.

McQuade et al. [27] found an association between increased survival and obesity in male patients under targeted and immune therapies for metastatic melanoma while Choi et al. [28], in a meta-analysis of nephrectomised renal cell cancer (RCC) patients, identified preoperative obesity as an independent prognostic factor for increased OS and cancer-specific survival (CSS).

Rodge et al. [29] found that notwithstanding more frequent post-op complications, obese patients had a statistically significant increased CSS among RCC patients subjected to surgery, and Schrader and colleagues [30] found an association between being overweight and improved CSS in organ confined RCC.

In patients with good performance status, Tsang et al. [31] demonstrated obesity to be linked to less mortality in patients with distant metastases from varied neoplasms.

Recent studies have tried to understand the reason behind higher BMI and better cancer outcomes.

In a cohort study from five different clinical studies, Sanchez et al. [32] aimed to assess differences in transcriptomics between tumour and peritumour tissue of both local and metastasized clear cell RCC of normal-weight and obese patients. Differences in tumour microenvironment were found with higher angiogenic scores and increased peritumoural inflammation encountered in specimen from obese individuals.

Albiges et al. [33] reported increased OS in obese RCC patients and established an inverse relationship between fatty acid synthase (FASN) expression and increased survival; FASN gene expression was downregulated in obese patients.

FASN has been linked to altered tumour biological behaviour both in RCC and gliomas [34].

Hakimi et al. [35] showed higher BMI to be linked to increased OS in RCC on univariate analysis, and most importantly, genome-wide studies revealed statistically significant upregulation of FASN in normal-weight patients while downregulated in obese individuals. In that study, FASN overexpression was also associated with decreased survival.

Zhao et al. [36] found fatty acid synthase to be increased in glioma cells while Grube and colleagues [37] reported a linear relationship between increased FASN expression and higher tumour grade and propose FASN inhibition as a target for glioma therapy.

Given the aforementioned findings regarding tumour biology of different neoplasms, we hypothesize that tumour microenvironment might be altered in obese patients, in particular with regard to fatty acid metabolism and angiogenesis.

Thus, the longer survival and progression-free survival experienced by our obese glioblastoma patient subgroup might be explained by obesogenic-induced tumour microenvironment change.

Better tolerance to chemoradiotherapy, higher energy reserves and lower tendency for cachexia [38] might have also contributed to the trend of increasing BMI associated with higher survival observed in our study.

General considerations

Our study is not devoid of shortcomings: it is a retrospective study, MGMT promoter gene methylation status was not accounted for and albeit the most used in clinical practice, BMI still remains an imperfect measurement of body adiposity, particularly in the overweight that constitutes the main bulk of our patients.

Conclusion

Excess body weight and obesity remain a public health problem due to the negative impact on cardiovascular health and increased cancer risk.

However, in similar fashion to multiple studies in various neoplasms, our glioblastoma patients with higher BMI fared better in terms of overall survival and progression-free survival than normal-weight patients.

Consequently, establishing a definitive link between excess body weight and increased cancer survival in prospective studies is of crucial importance.

Transcriptomics, proteomics and metabolomics are among the tools currently available to ascertain differences in glioblastoma microenvironment of obese patients that might explain the more indolent disease course. A better understanding of tumour pathogenesis and biological behaviour within this subgroup might result in better patient outcome through identification of novel molecular and therapeutic targets.

Author contributions Guarantor of integrity of the entire study: PVA. Study concepts and design: PVA and PL. Literature research: PVA and PL. Clinical studies: PVA. Experimental studies/data analysis: PVA and BDC. Statistical analysis: PVA and BDC. Manuscript preparation: PVA, PL and RV. Manuscript editing: PL and RV.

Data availability All datasets generated for this manuscript can be obtained from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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