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Association between body mass index and mortality in patients with glioblastoma multiforme

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Abstract

Purpose—To examine the association between obesity and survival in patients with glioblastoma multiforme (GBM)

Methods—Using a prospective design, 1,259 patients with previously untreated GBM were recruited between 1991 and 2008. Height and weight were self-reported or abstracted from medical records at study entry and used to calculate body mass index (BMI) [weight (kg)/height (m)]². Cox proportional models were used to estimate the risk of death associated with BMI as a

continuous variable or categorized using established criteria (normal weight, 18.5–24.9 kg/m²; overweight, 25.0–29.9 kg/m²; obese, ≥30.0 kg/m²).

Results—Median follow-up was 40 months, and 1,069 (85%) deaths were observed during this period. For all patients, minimal adjusted analyses indicated no significant association between BMI treated as a continuous variable and survival. Compared with patients with a BMI 18.5–24.9 kg/m², the minimally adjusted HR for overall survival was 1.08 (95% CI, 0.94–1.24) for a BMI 25–29.9 kg/m² and 1.08 (95% CI, 0.91–1.28) for a BMI ≥30.0 kg/m². After additional adjustment for adjuvant therapy, the HR for those with a BMI of 25.0–29.9 kg/m² was 1.14 (95% CI, 0.99–1.32) and 1.09 (95% CI, 0.91–1.30) for those with a BMI ≥30.0 kg/m². No significant interactions were revealed for BMI and any demographic variables.

Conclusion—BMI was not associated with survival in newly diagnosed and previously untreated patients with GBM. Further research investigating the prognostic significance of alternative, quantitative measures of *body habitus*, and functional performance are required.

Keywords

Epidemiology; Glioblastoma; Survival; Prognosis; Body weight; Energy balance

Introduction

Glioblastoma multiforme (GBM) remains one of the greatest challenges in oncology today [1]. Despite significant advancements in treatment, concomitant improvements in survival have been poor with an overall 1-year survival rate of 17.7% [2–4]. Further, there is considerable survival variability due to the heterogeneous features of disease pathophysiology and broad range of clinical comorbid conditions at presentation. Thus, identifying accurate markers of prognosis to optimize treatment and survival outcomes is of major clinical importance [5]. One relatively simple, currently unstudied, factor that may be associated with prognosis in primary GBM is body mass index (BMI).

BMI is widely used as an indicator of total body fat (adiposity) and is calculated using weight in kilograms divided by the square of the height in meters (kg/m²). A BMI ≥25 or ≥30 kg/m² is strongly associated with increased risk of several forms of cancer [6–8] including primary malignant glioma. Following diagnosis, obesity has been shown to be associated with worse prognosis [9–14] in patients with early and advanced malignancy; however, several studies have also described a phenomenon known as the ‘obesity paradox’ wherein an elevated BMI is associated with longer survival in certain cancer scenarios including lung [15], oral cavity and pharynx [16], and castrate-resistant metastatic prostate cancer [17, 18]. The association, and direction, of the association between BMI and survival in patients with primary glioma has not been investigated. To clarify this issue, we investigated the prognostic significance of BMI (at diagnosis) on overall survival in patients with newly diagnosed primary malignant GBM.

Materials and methods

Participants and setting

Full details regarding the study sample, recruitment, and procedures have been reported previously [19]. In brief, patients with histologically confirmed, clinically stable, and previously untreated GBM (WHO grade IV) were recruited at the University of California at San Francisco (UCSF) and Duke University Medical Center (DUMC). The Institutional Review Board at both participating institutions approved the study, and written informed consent was obtained from all participants prior to initiation of any study procedures. In the San Francisco Bay Area Adult Glioma Study, cases ≥20 years and residing in the San

San Francisco Bay Area were identified using the regional cancer registry's rapid case ascertainment system during three ascertainment periods: August 1991 to April 1994 (Series I), May 1997 to August 2000 (Series II), and November 2001 to September 2004 (Series III). In the DUMC study, cases < 18 years were recruited during two periods: Pilot study (2003–2006) and Main study (2006–2008). Height and weight were either self-reported or abstracted from medical records at the time of diagnosis in the UCSF and DUMC studies, respectively, and used to calculate BMI [weight (kg)/height (m)]². Information on treatment in both studies was extracted from the medical records.

Follow-up

GBM cases were followed for survival status through February 5, 2008, in the San Francisco Bay Area Adult Glioma Study and through August 27, 2009, in the DUMC study.

Statistical considerations

Statistical analysis was performed in SAS v9.2 (SAS Institute, Cary, NC). Kaplan–Meier methods (PROC LIFETEST) were used to compute median survival. Other descriptive statistics were generated using PROC TABULATE. Cox proportional hazard models (PROC PHREG) estimated relative hazard ratios (HR) and the 95% confidence intervals associated with BMI, either expressed as a continuous variable or categorized using accepted cut-points (normal weight, 18.5–24.9 kg/m²; overweight, 25.0–29.9 kg/m²; obese, ≥ 30.0 kg/m²). Hazard ratios associated with BMI were calculated for all subjects and for each ascertainment period within both studies. Minimally adjusted models for each period of ascertainment included age <60 years vs. ≥ 60 years, gender (male vs. female), and number of days between recorded BMI and diagnosis. To examine possible interactions between BMI and age and gender, interaction terms between BMI (continuous or BMI categories) and age (dichotomous variables with cutpoint at 60) or gender were introduced into the minimally adjusted models. Fully adjusted models included age (continuous), gender, race (white vs. non-white), radiation (any radiation vs. none), resection (total or partial resection vs. none), chemotherapy (chemotherapy including temodar, other chemotherapy without temodar, no chemotherapy), and number of days between recorded BMI and diagnosis. In addition to these variables, the models for all subjects included periods of ascertainment (four indicator variables accounting for Series I–III, the Pilot and the Main studies). Finally, given that the average time from diagnosis to study entry was 4 months, we conducted a sensitivity analysis removing cases recruited ≥ 6 months after primary diagnosis.

Results

Participant recruitment took place between January 1991 and April 2008. In brief, a total of 1,259 patients were recruited during the study period.

Baseline characteristics

The participant demographic and clinical characteristics are shown in Table 1. For the entire sample, BMI was 26.6 ± 4.8 kg/m² with 39, 40, and 20% being classified as normal, overweight, and obese, respectively. Sixty-three percent of BMI was obtained via self-report (i.e., all cases obtained from UCSF), while 37% was abstracted from medical records (i.e., all cases from DUMC). Mean age at diagnosis was 58 ± 13 years, 61% were men, 78% underwent partial or total resection, and 46% received temodar-containing adjuvant chemotherapy. There were several differences between study sites. Patients recruited at DUMC were younger, more likely to be men and white. Similarly, DUMC patients were more likely to undergo partial/total resection while a lower proportion received radiation treatment (*P*s < 0.05). A time trend concerning the increasing use of temodar was observed in both study sites [Table 1]. Overweight (BMI 25–29.9 kg/m²) patients were more likely to

be men ($P < 0.05$). There were no significant differences in any other demographic or clinical variable on the basis of BMI.

BMI and overall survival

Median follow-up was 40 months. During this period, 1,069 deaths were recorded (85% of the total sample). Overall, median survival was 379 days. For the entire sample, minimal adjusted analyses (adjusted for age, gender, and days between diagnosis and study entry) indicated no significant association between BMI treated as a continuous variable and survival in any study cohort (Table 2). When treated as a categorical variable, compared with patients with a BMI 18.5–24.9 kg/m², the minimally adjusted HR for overall survival for the entire sample was 1.08 (95% CI, 0.94–2.4) for a BMI 25–29.9 kg/m² and 1.08 (95% CI, 0.91–1.28) for a BMI ≥ 30.0 kg/m² (Table 2; Fig. 1, plot F). Similar nonsignificant results were indicated for all study Series except UCSF Series I (Fig. 1, plots A–E). In this cohort, compared with patients with a BMI 18.5–24.9 kg/m², the minimally adjusted HR for overall survival was 1.25 (95% CI, 0.94–1.66) for a BMI 25.0–29.9 kg/m² and 1.55 (95% CI, 1.06–2.28) for a BMI ≥ 30.0 kg/m² (Fig. 1).

We also examined whether the relationship between BMI and overall survival was sensitive to the additional adjustment for surgical resection and adjuvant therapy (Table 2). We observed no linear trend for BMI, when treated as a continuous variable, and overall survival. For all patients, the HR for those with a BMI of 25.0–29.9 kg/m² was 1.14 (95% CI, 0.99–1.32) and 1.09 (95% CI, 0.91–1.30) for those with a BMI ≥ 30.0 kg/m². As before, significant findings were only indicated in UCSF Series I. In this cohort, compared with patients with a BMI 18.5–24.9 kg/m², the HR for overall survival was 1.37 (95% CI, 1.03–1.84) for a BMI 25.0–29.9 kg/m² and 1.54 (95% CI, 1.04–2.27) for a BMI ≥ 30.0 kg/m². No significant interactions were revealed for BMI and demographic variables, specifically, age and gender. Finally, a total of 168 patients were recruited 6 months after primary diagnosis leaving a total sample of 1,094. For the entire sample, minimal adjusted analyses (adjusted for age, gender, and days between diagnosis and study entry) indicated no significant association between BMI treated as a continuous variable and survival in any study cohort. Similar nonsignificant results were also observed when BMI was treated as a categorical variable (data not presented).

Discussion

The results of this study indicated, in general, no significant relationship between BMI and survival in newly diagnosed and previously untreated patients with GBM across multiple study cohorts. Specifically, analyses including all patients indicated that obesity conferred between a non-significant 8 and 14% increase risk of mortality, relative to normal weight subjects. In Series I, obesity conferred a 25–54% significant increased risk of mortality, relative to normal weight patients although this study series contributed a small portion of patients in comparison with the overall study sample. In addition, Series I was conducted in the early 1990s with fundamental differences in patient management relative to present day; thus, the implications of these findings are unclear.

Over the past two decades, numerous studies report that elevated BMI is consistently associated with higher incidence of several forms of solid and myeloid tumors [8]. The majority of work in this setting has been conducted in breast cancer with results indicating that, in general, overweight or obese women have a 10–25 and a 20–40% increased risk of death, respectively, relative to normal weight women [20]. In contrast, however, several studies have found that obesity is associated with longer survival, relative to normal or underweight cancer patients. For example, Halabi and colleagues [17] found that compared

with men with normal BMIs ($<25.0 \text{ kg/m}^2$), overweight men had a 20% reduction in the risk of death in an observational study of 1,226 men with castrate-resistant prostate cancer.

These opposing findings highlight the opposing nature of BMI as a measure of adiposity in patients with solid malignancies. On one hand, an elevated BMI ($>25 \text{ kg/m}^2$), which reflects excess adiposity, is associated with worse prognosis in certain oncology scenarios via elevated circulating concentrations of metabolic and pro-inflammatory hormones that are postulated to stimulate tumor progression and metastasis. On the other hand, elevated BMI is also, typically, associated with greater muscle (lean) mass, which acts as a potent source of energy reserve and thus better prognosis in patients with advanced malignancy suffering disease or treatment-related muscle wasting (i.e., the 'obesity paradox'). Taken together, even if elevated adiposity associated with worse survival or vice versa, the BMI-survival relationship could still be null since it reflects both adiposity and lean mass; this suggests that alternative measurement tools are required to adequately characterize important physiologic changes that occur in cancer patients undergoing aggressive systemic and supportive care therapies.

To address this concern, several research groups, including our own, have started to investigate the utility of measurement tools that provide a sensitive and quantitative physiologic measurement of organ components that govern human energetics (e.g., skeletal muscle and visceral adipose tissue, whole-body oxygen consumption, etc.) [21–24]. In a series of studies, Sawyer and colleagues [22–24] report that measures of skeletal muscle mass and sarcopenia, as assessed via computerized tomography, are a significant predictor of treatment toxicity, symptoms, and disease progression across several advanced solid malignancies. Our group observed that postsurgical primary malignant glioma patients have markedly reduced exercise capacity ($\text{VO}_{2\text{peak}}$), isokinetic strength, and muscle cross-sectional area; these parameters were associated with patient-reported outcomes and also may identify a subgroup of patients at higher risk of progressive disease or death [25]. Finally, our group recently found that $\text{VO}_{2\text{peak}}$ is also a strong independent predictor of long-term overall survival in 398 NSCLC even after controlling for traditional prognostic factors.

Intriguingly, Derr et al. [26] reported that hyperglycemia (blood glucose $>94 \text{ mg/dL}$) was associated with a 29–57% increased risk of death in 191 newly diagnosed GBM patients, independent of BMI. Metabolic ligands such as glucose, insulin, and other members of the insulin-like growth family are important growth factors for solid tumor development and progression [27]. Approximately 80% of glucose disposal occurs in the skeletal muscles, whereas $\text{VO}_{2\text{peak}}$ and physical activity are inversely associated with circulating concentrations of metabolic hormones. As such, changes in systemic levels of metabolic hormones may be one mediating biological mechanism underpinning the *body habitus/functional performance*–prognosis relationship in cancer. Prospective studies investigating the prognostic importance of quantitative physiologic assessment together with correlative studies that provide insight into underlying mechanism(s) in GBM are warranted.

The most important limitation of this study is that our measure of weight status was BMI that may provide an imprecise measurement of body composition. *Body habitus* is heterogeneous and distribution of adiposity as well as lean to body fat mass ratio in relation to functional performance ability will likely provide more accurate insight regarding the association between *body habitus* and prognosis in GBM. Another important limitation is self-report acquisition of BMI in a proportion of patients in this study.

In summary, in this large, prospective multi-center study, we observed no relationship between BMI and survival in newly diagnosed and previously untreated patients with GBM.

Future research is required investigating the prognostic significance of alternative, quantitative measures of body composition and functional performance in GBM and other advanced solid malignancies.

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Fig. 1.

Panel figure showing Kaplan–Meier survival curves for overall survival by BMI (unadjusted) by study series. **a** UCSF Series I (1991–1994) ($n = 247$), **b** UCSF Series II (1997–1999) ($n = 228$), **c** UCSF Series III (2001–2004) ($n = 325$), **d** DUMC Pilot (2003–2006) ($n = 116$), **e** DUMC Main (2006–2008) ($n = 343$), and **f** All Patients ($n = 1,259$)

Table 1

Participant characteristics of 1,259 patients with previously untreated primary malignant glioblastoma multiforme

	All	UCSF			DUMC		Comparison between groups
		Series I (1991–1994)	Series II (1997–2000)	Series III (2001–2004)	Pilot (2003–2006)	Main (2006–2008)	
Number of GM cases/censored (non-deceased)	1,259/190	247/2	228/1	325/34	116/27	343/126	
Median survival (days)	379	209	241	327	752	576	<0.0001 ^b
Days from diagnosis to study entry ^a	116.1 (131.7)	182.6 (184)	124.7 (104.8)	132.2 (149.9)	68.3 (54.1)	53.5 (50.3)	<0.0001 ^c
<u>Demographics</u>							
Age at diagnosis (years)	58 [13]	61 [14]	61 [13]	60 [14]	52 [12]	55 [11]	<0.0001 ^c
Males (%)	61	55	58	58	66	68	<0.0048 ^d
White (%)	87	84	84	78	97	95	<0.0001 ^d
<u>Therapy</u>							
Resection (partial or total) (%)	78	70	76	73	91	82	<0.0001 ^d
Radiation therapy (%)	81	80	87	86	74	76	<0.0001 ^d
Temodar-containing chemotherapy (%)	46	0	2	63	71	85	<0.0001 ^d
Non-Temodar-containing chemotherapy (%)	12	10	23	5	19	11	<0.0001 ^d
<u>Anthropometrics</u>							
Weight (kg)	78.9 (17.5)	74.8 (17.4)	77.6 (17.5)	78.4 (16.3)	81.0 (15.6)	82.3 (17.0)	<0.0001 ^c
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	<0.0001 ^c
BMI (kg/m ²)	26.6 (4.8)	25.4 (4.7)	26.1 (5.0)	26.6 (4.7)	26.9 (4.5)	27.7 (4.9)	<0.0001 ^c
Underweight (<18.5 kg/m ²) (%)	1	2	3	1	1	0	
Normal weight (18.5–24.9 kg/m ²) (%)	39	48	44	42	34	29	
Overweight (25.0–29.9 kg/m ²) (%)	40	36	35	40	45	45	
Obese (≥30.0 kg/m ²) (%)	20	14	18	18	20	27	<0.0001 ^d

^aDescriptive statistics for the continuous variables are presented by mean values and (standard deviation)

^bLogrank test

^cANOVA

^dChi-square test

Table 2

Association between BMI and survival in 1,259 patients with previously untreated primary malignant glioblastoma multiforme

Models	Hazard ratio (95% confidence interval limits)					
	All ^c	USCF			DUMC	
		Series I (1991–1994)	Series II (1997–1999)	Series III (2001–2004)	Pilot (2003–2006)	Main (2006–2008)
<u>Minimally adjusted^a</u>						
BMI, continuous (kg/m ²)	1.00 (0.99–1.01)	1.03 (1.00–1.05)	0.99 (0.97–1.01)	1.00 (0.98–1.03)	0.99 (0.95–1.04)	1.00 (0.98–1.03)
BMI, categories						
Normal weight (18.5–24.9 kg/m ²)	Reference	Reference	Reference	Reference	Reference	Reference
Overweight (25.0–29.9 kg/m ²)	1.08 (0.94–1.24)	1.25 (0.94–1.66)	1.00 (0.74–1.36)	1.06 (0.82–1.38)	0.92 (0.57–1.50)	1.07 (0.77–1.50)
Obese (≥ 30.0 kg/m ²)	1.08 (0.91–1.28)	1.55 (1.06–2.28)	0.94 (0.65–1.35)	1.08 (0.78–1.50)	0.86 (0.48–1.57)	1.01 (0.69–1.47)
<u>Fully adjusted^b</u>						
BMI, continuous (kg/m ²)	1.01 (0.99–1.02)	1.02 (1.00–1.05)	1.00 (0.97–1.02)	1.00 (0.97–1.03)	0.99 (0.94–1.04)	1.01 (0.98–1.04)
BMI, categories						
Normal Weight (18.5–24.9 kg/m ²)	Reference	Reference	Reference	Reference	Reference	Reference
Overweight (25.0–29.9 kg/m ²)	1.14 (0.99–1.32)	1.37 (1.03–1.84)	1.19 (0.8–1.65)	1.15 (0.86–1.54)	0.77 (0.46–1.30)	1.15 (0.86–1.54)
Obese (≥ 30.0 kg/m ²)	1.09 (0.91–1.30)	1.54 (1.04–2.27)	0.95 (0.65–1.39)	1.05 (0.72–1.52)	0.78 (0.41–1.49)	1.08 (0.73–1.59)

^a Adjusted for age, gender, and days between diagnosis and study entry

^b Adjusted for age, gender, race, days between diagnosis and entry, and treatment (resection, radiation, chemotherapy with Temodar, chemotherapy without Temodar)

^c Models were additionally adjusted for sites and study period