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Clinical Investigation

Body Mass Index as a Prognostic Marker in Glioblastoma Multiforme: A Clinical Outcome

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Summary

This study deals with the important subject of obesity and its impact on survival in glioblastoma patients. This is a single institution retrospective study with a fairly large sample size (392 patients), treated on a uniform protocol with a long-term follow-up. Elevated BMI patients appear to have a better survival.

Purpose: Correlation of body mass index (BMI) with clinical outcome in patients with glioblastoma is not well documented. Hence, we studied the association between survival and pretreatment BMI in glioblastoma patients.

Methods and Materials: In this retrospective study, only patients with histopathology-confirmed glioblastoma were included. Their BMIs were calculated from height and weight measurements and recorded in medical records at their first examination. Treatment plans for all patients consisted of concurrent radiation therapy and temozolomide, followed by maintenance therapy with temozolomide. The primary endpoint was overall survival (OS). Univariate and multivariate Cox proportional hazards models were used to estimate the mortality risk associated with BMI as a continuous and categorical variable. A BMI of 18.5 to 24.9 kg/m^2 was classified as normal, 25.0 to 29.9 kg/m^2 as overweight, and $\geq$30.0 kg/m^2 as obese.

Results: Data from 392 patients treated from January 2008 through June 2016 were analyzed. At a median follow-up of 48.6 months, the median OS was 13.5 months in normal subjects, 15.4 months in overweight subjects, and 15.1 months in obese subjects. A total of 81% of the patients died. The hazard ratios for overweight and obese patients were 0.70 (95% confidence interval, 0.54-0.92; $P = .009$) and 0.66 (95% confidence interval, 0.45-0.98; $P = .04$), respectively, when adjusted for age, Karnofsky performance score, and extent of resection. Sex, diabetes, and hypertension had no significant interactions.

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Conclusions: Patients with elevated BMIs had significantly better OS in our series of patients. The mechanism of this interaction needs to be explored further to understand this association.

Introduction

Body mass index (BMI) is a simple surrogate for measuring the approximate adiposity in the human body. The association between obesity and all-cause mortality is complex. A few studies suggest that being overweight confers either a small benefit or a negligible effect on mortality (1, 2), whereas other studies report a small increased risk (3). In the present study, we examined the impact of BMI on overall survival (OS) and BMI as a useful prognostic marker in patients with glioblastoma multiforme (GBM).

Methods and Materials

Medical records of 392 patients treated between January 2008 and June 2016 in our center were retrospectively analyzed. Follow-up data were available until the end of September 2017, by which time, 80.9% patients had died. All patients underwent standard treatment for GBM, consisting of maximal safe surgical resection, concurrent radiation therapy plus temozolomide, followed by 6 cycles of adjuvant temozolomide (4). Surgery was categorized as biopsy (<10% resected), subtotal resection (10%−90% resected), and gross total resection (>90% resected). Height and weight measurements of patients recorded at the time of first admission were used for calculating BMI.

Statistical analysis was performed using SPSS version 20 software (SPSS Statistics). Kaplan-Meier analysis was performed to compute OS by using the log-rank test. Survival duration was calculated from the date of surgery to the date of death from any cause or date of last contact. Univariate and multivariate Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The primary endpoint was OS, and a P value less than .05 was considered statistically significant.

Table 1 Baseline characteristics of 392 patients with newly diagnosed histopathologically confirmed glioblastoma multiforme

Prognostic factor	Number of patients	Percentage of patients	Median	Range	Number of events*	Percentage of events
Age						
18-54 (y)	156	39.8	56.0	64.0 (18-82)	127	81.4
≥55 (y)	236	60.2			190	80.5
Sex						
Males	269	68.6			218	81.0
Females	123	31.4			99	80.5
Karnofsky performance score						
≥80	134	34.2			107	79.9
≥60 and <80	149	38.0			124	83.2
≥40 and <60	109	27.8			86	78.9
Body mass index (kg/m^2)						
18.5-24.9	209	53.3	24.3	26.9 (16.6-43.5)	175	83.7
25.0-29.9	143	36.5			110	76.9
≥30.0	40	10.2			32	80.0
Recursive partitioning analysis						
Class 3	44	10.8			32	72.7
Class 4	183	46.7			152	83.1
Classes 5 and 6	165	42.1			133	80.6
Diabetes						
Nondiabetic	287	73.2			231	80.5
Diabetic	105	26.8			86	81.9
Hypertension						
Nonhypertensive	264	67.3			217	82.2
Hypertensive	128	32.7			100	78.1
Extent of resection						
Biopsies	69	17.6			53	76.8
Subtotal	157	40.1			131	83.4
Gross total	166	42.3			133	80.1

* The term "event" refers to death.

Results

The median BMI was 24.3 (range, 18.5-43.5); 53.3% of patients had normal weight, 36.5% were overweight, and 10.2% were obese (Table 1). At a median follow-up of 48.6 months, median OS was 14.7 months. The 2-, 3-, and 5-year OS rates were 24.2%, 13.4%, and 6.9%, respectively. Only 6% of patients reported a significant weight loss (>5 kg) in the year preceding diagnosis. We did not find any significant association between socioeconomic status and being overweight or obese. A total of 359 patients (91.6%) completed planned adjuvant concurrent chemoradiation, and 273 patients (70%) completed 6 cycles of maintenance temozolomide therapy without any dose compromise.

Age, Karnofsky performance score, extent of surgical resection, recursive partitioning analysis class, and BMI were all significant independent predictors for survival in unadjusted analysis (Table 2) (5-7). When BMI was analyzed as a categorical variable, the unadjusted HRs for death in overweight and obese subjects were 0.62 (95% CI, 0.49-0.79; $P < .001$) and 0.65 (95% CI, 0.44-0.95; $P = .026$), respectively, compared to subjects whose BMI was normal. The corresponding HRs adjusted for overweight and obese patients were 0.70 (95% CI, 0.54-0.92; $P = .009$) and 0.66 (95% CI, 0.45-0.98; $P = .04$) respectively.

Figure 1 shows the Kaplan-Meier survival curves for age as a categorical variable, sex, Karnofsky performance score, extent of resection, BMI as a categorical variable, and recursive partitioning analysis result. A log rank test was run to understand the different survival distribution among the various prognostic categories (Table 3). The median periods of OS were 13.5, 15.4, and 15.1 months in normal, overweight, and obese subjects, respectively, with a $\chi^2(2)$ value of 17.34 ($P < .001$). There was a statistically significant difference between survival distribution for normal subjects and that for overweight subjects, with a $\chi^2(1)$ value of 15.89 ($P < .001$) but not between normal and

Table 2 Adjusted and unadjusted Cox proportional hazard analysis

Prognostic factor	Unadjusted Cox analysis		Adjusted Cox analysis†		Adjusted Cox analysis‡	
	P value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)
Continuous age	.002	1.01 (1.00-1.02)				
Age						
18-54 (y)*						
≥55 (y)	<.001	1.63 (1.30-2.04)	.001	1.47 (1.16-1.87)		
Sex						
Males*						
Females	.291	0.88 (0.69-1.12)				
Continuous body mass index (kg/m^2)	.001	0.95 (0.92-0.98)				
Categorical body mass index (kg/m^2)	<.001		.014		.002	
18.5-24.9*						
25.0-29.9	<.001	0.62 (0.49-0.79)	.009	0.70 (0.54-0.92)	.001	0.66 (0.52-0.85)
≥30.0	.026	0.65 (0.44-0.95)	.038	0.66 (0.45-0.98)	.048	0.68 (0.47-0.99)
Karnofsky performance score	<.001		<.001			
≥80*						
≥60 and <80	.004	1.46 (1.13-1.90)	.463	1.12 (0.83-1.49)		
≥40 and <60	<.001	2.26 (1.69-3.01)	<.001	1.98 (1.46-2.68)		
Recursive partitioning analysis	<.001				<.001	
Class 3*						
Class 4	.004	1.77 (1.20-2.59)			.009	1.67 (1.13-2.45)
Class 5 and 6	<.001	3.30 (2.22-4.91)			<.001	3.58 (2.07-4.59)
Diabetes						
Nondiabetic*						
Diabetic	.347	1.126 (0.88-1.44)				
Hypertension						
Nonhypertensive*						
Hypertensive	.530	0.93 (0.73-1.18)				
Extent of resection	<.001		.001			
Biopsy*						
Subtotal	.085	0.76 (0.55-1.04)	.070	0.74 (0.54-1.03)		
Gross total	<.001	0.49 (0.35-0.68)	<.001	0.53 (0.38-0.74)		

Abbreviations: CI = confidence interval; HR = hazard ratio.

* Referent category.

† Body mass index adjusted for age, Karnofsky performance score, and extent of resection.

‡ Body mass index adjusted for recursive partitioning analysis.

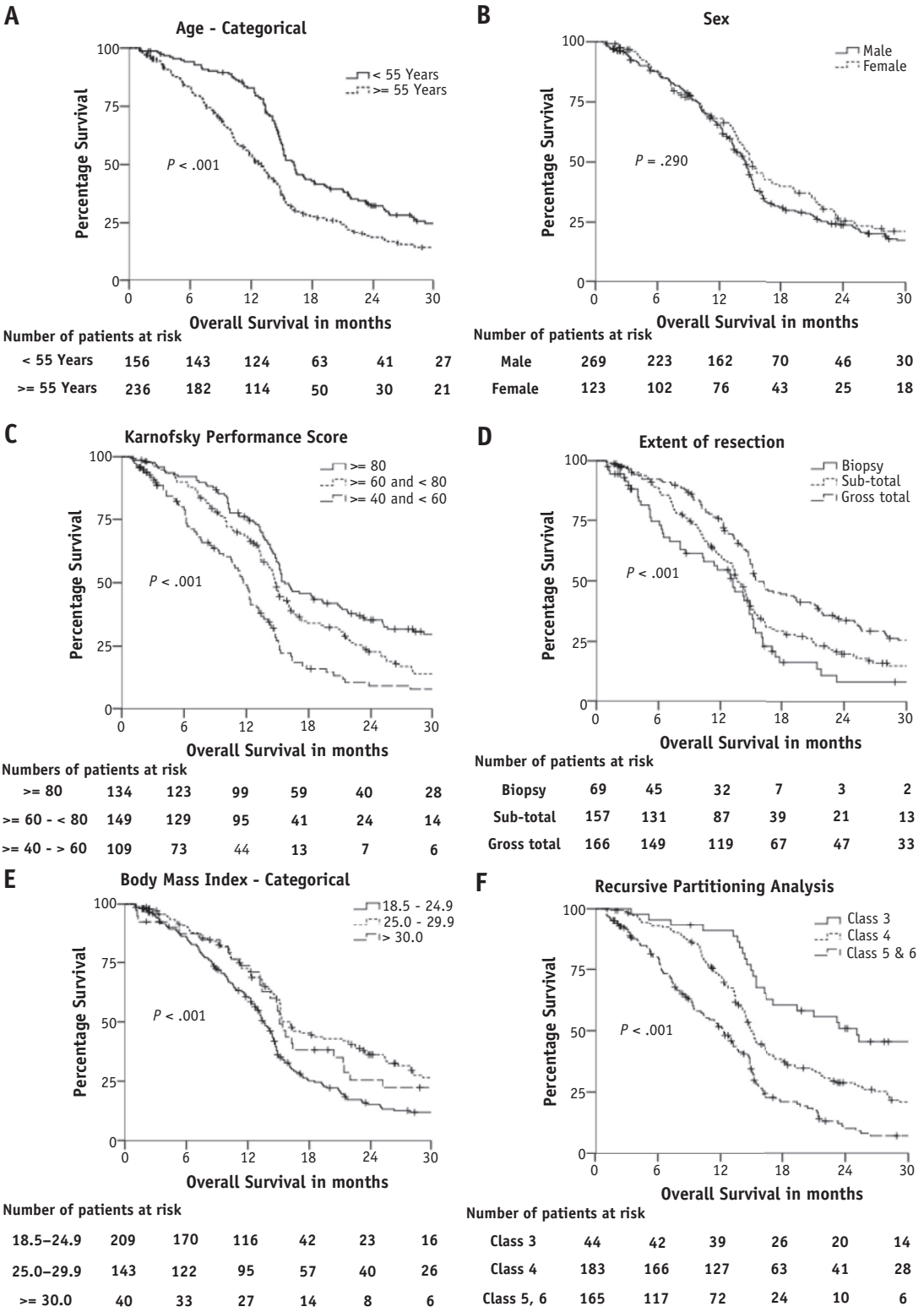

Fig. 1. Kaplan-Meier survival plots. (A) Categorial age; (B) Sex; (C) Karnofsky performance score; (D) extent of resection; (E) categorical body mass index; (F) recursive partitioning analysis.

Table 3 Kaplan-Meier pairwise comparisons by log rank (Mantel-Cox)

Prognostic factors	Median overall survival	χ^2	*P* value*	χ^2	*P* value*	χ^2	*P* value*
Karnofsky performance score		≥80		≥60 but <80		<60	
≥80	15.7			9.091	**.003**	28.801	**.000**
≥60 and <80	14.8	9.091	**.003**			9.502	**.002**
≥40 and <60	11.7	28.801	**.000**	9.502	**.002**		
Extent of resection		Biopsy		Subtotal		Gross total	
Biopsy	13.2			2.806	.094	18.929	**.000**
Subtotal	13.6	2.806	.094			12.457	**.000**
Gross total	15.7	18.929	**.000**	12.457	**.000**		
Recursive partitioning analysis		Class 3		Class 4		Classes 5 and 6	
Class 3	25.1			8.988	**.003**	37.036	**.000**
Class 4	14.9	8.988	**.003**			25.960	**.000**
Classes 5 and 6	12.3	37.036	**.000**	25.960	**.000**		
Categorical body mass index (kg/m^2)		18.5-24.9		25.0-29.9		>30.0	
18.5-24.9	13.5			15.885	**.000**	4.422	.035
25.0-29.9	15.4	15.885	**.000**			.024	.878
>30.0	15.1	4.422	.035	.024	.878		

* Categories that are significantly different after applying Bonferroni correction are shown in boldface type.

obese subjects, with $\chi^2(1)$ value of 4.42 ($P = .035$) and between overweight and obese subjects, with a $\chi^2(1)$ value of 0.024 ($P = .878$).

When BMI was evaluated as a continuous variable, it gave an HR of 0.95 (95% CI, 0.92-0.98; $P = .001$) in both univariate and multivariate models.

Discussion

There are conflicting reports of the association between obesity and cancer incidence and mortality. Obesity has been extensively associated with higher incidence in several types of solid tumors (8-10) and hematologic malignancies (11-13). Obesity has been associated with higher incidence of breast cancer and esophageal cancer and a worse prognosis regardless of tumor subtype (14-16). By contrast, leanness has been associated with increased incidence of lung (17-23) and oral cancers (24, 25) in some case-control and cohort studies. One of the conclusions drawn from the studies cited above was that the inverse association between BMI and the incidence of lung or oral cancer might have been due to residual effects of smoking and chronic lung disease rather than leanness.

Sergentanis et al (26) reported obesity as a risk factor for overall brain and central nervous system tumors, meningiomas, and gliomas among female patients. Similarly, a higher incidence of meningiomas was found by Weidman et al (27), but they did not find any association between BMI and risk of glioma. There are few studies that correlate BMI with overall survival in GBM patients. Jones et al (28) did not find any association between BMI and survival in 1259 GBM patients previously untreated between 1991 and 2008. It is important to note that treatment protocols changed over that period and that height and weight were self-reported by the patients, which may have resulted in misclassification of BMI category. Siegel et al (29) examined 853 patients in a case-control study to evaluate association of prediagnostic body weight 1 to 5 years prior to diagnosis and survival in high-grade glioma patients. The authors reported reduced OS in underweight and obese patients compared with patients of normal weight. Also, in that study, all body measurements were self-reported. Additionally, there was missing information for performance status and nature of surgery, which could have affected the efficacy of multivariate analysis in detecting the actual association between BMI and survival outcome. In the present study, overweight and obese GBM patients had better rates of OS than normal weight patients, in contrast to those reported by Jones et al (28) and Siegel et al (29). There were no significant differences in survival between diabetic and nondiabetic subjects (14.4 vs 14.8 months, respectively; $P = .343$). In contrast, Chambless et al (30) reported elevated BMI and diabetes as independent risk factors for poor outcome in 171 patients with high-grade glioma. In the present study, the median survival benefit was 1.9 months in overweight subjects and 1.6 months in obese subjects compared with that of the normal BMI subjects. To our knowledge, this is the first study to report improved survival in GBM patients with elevated BMI.

Some authors have coined the term "obesity paradox" for this intriguing association between increased BMI and improved survival. A common explanation given for the obesity paradox is "collider stratification bias." The protective effect of obesity may be mediated by stronger immune and inflammatory responses in obese patients. This has been reported in patients with community-acquired

pneumonia, when obese patients had higher survival rates than nonobese patients (31). However, to our knowledge there has been no similar study conducted in cancer patients.

The strengths of this study include a moderately large sample size, single-institution study with uniform treatment protocol over the study period, and histopathologic confirmation of all cases. The main limitations of this study are the inherent drawback of retrospective data analysis and the unavailability of O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status in the study population. It may also be argued that BMI is not the best measurement of adiposity, as it does not discriminate between muscle mass and adipose tissue, abdominal and hip area fat, and visceral and deep abdominal fat.

Conclusions

The interaction between BMI and survival in GBM patients is complex and requires further research to evaluate the factors leading to a better outcome in patients with elevated BMI.

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