Original Study

Role of Overweight, Obesity, and Comorbidities in the Prognosis of Patients With Breast Cancer With Brain Metastases

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Abstract

Brain metastases from breast cancer occur in 20% to 30% of patients, with a short overall survival. Some have previously postulated a role of overweight, obesity, and diabetes in their prognosis. A database analysis from 2 referral centers with 228 patients failed to identify an association between weight or diabetes mellitus in patients with metastatic breast cancer.

Introduction: Breast cancer (BC) is the most common cancer in women, and the incidence of brain metastasis (BM) from BC ranges from 20% to 30%, with a median survival of 10 to 15 months. Previous reports have shown that the presence of obesity or diabetes negatively impacts survival. The present study investigates the association between obesity or diabetes mellitus (DM) and overall survival of patients with BC with BM. **Materials and Methods:** A database from 2 referral centers for the period of July 2014 to February 2018 was analyzed. The inclusion criteria were as follows: patients who had a confirmed diagnosis of BC with BM were followed and treated at these centers. Demographic data, body weight and height, clinical and oncologic history, functional status, prognostic scales, and prognoses were examined. **Results:** A total of 228 patients were included. The median age at BM was 50 years; the median survival after diagnosis was 12.1 months; 108 patients had a body mass index (BMI) $\geq$ 25, and 40 (17%) patients had DM. The association between survival and the presence of BMI $>$ 25 exhibited a *P* value of 0.3. **Discussion:** We found no association between overweight, obesity, or DM and survival in patients with BC with BM. The role of obesity in cancer is a robust research topic, as there are many questions to be answered. **Conclusion:** Obesity as a prognostic indicator should be further studied, because we found no association between overall survival and either patients with BM from BC with a BMI $>$ 25 or those with normal weight.

Clinical Breast Cancer, Vol. 19, No. 2, e394-8
Keywords: Breast cancer, Brain metastases, Overweight, Prognosis, Survival

Introduction

Breast cancer (BC) is the most common cancer in women.[1] The incidence of brain metastasis (BM) from BC ranges from 20% to 30% and is increasing owing to advances in imaging technologies, which have led to earlier detection of BM and the introduction of novel therapies, resulting in longer survival. Overall survival after the diagnosis of BM ranges from 1 to 55 months and has been shown to be affected by characteristics such as multiple metastases, the presence of extracranial metastases, BM size, Karnofsky performance score (KPS), and triple-negative subtype, all of which indicate reduced survival.[2]

A recent study reported that an elevated body mass index (BMI) or diabetes also negatively impacted survival in 84 patients with BM from BC.[3] This link between a reduction in survival and obesity in patients with BC has been reported by other researchers.[4] Multiple mechanisms have been proposed, including the role of menopause, a reduction in the effective chemotherapy dose, and the genetics and histology of BC.[5] Most of the studies that focused on weight as a prognostic indicator did not include metastatic BC, and evidence concerning the role of elevated weight in BM from BC is infrequently reported. We therefore designed a study to investigate the association of overweight, obesity, normal weight, and diabetes with overall survival in patients with BC with BM.

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Submitted: Nov 2, 2018; Revised: Dec 29, 2018; Accepted: Dec 29, 2018; Epub: Jan 7, 2019

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1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2018.12.018

Material and Methods

A prospectively acquired database from 2 referral centers in Mexico City (Instituto Nacional de Cancerología and Instituto Nacional de Neurología y Neurocirugía) from July 2014 to February 2018 was created. The inclusion criteria included women with a confirmed diagnosis of BC, BM confirmed by magnetic resonance imaging (MRI), height and weight recorded at the time of BM diagnosis, and at least 2 determinations of serum glucose, hemoglobin A1c, and lipid profiles. The exclusion criteria included previous steroid use, incomplete records, or patients not treated by any of the neuro-oncology unit personnel. Diabetes was diagnosed according to the American Diabetes Association recommendations,[6] hypertension was diagnosed according to the Joint National Committee 8 criteria,[7] overweight was classified based on a BMI of 25 to 29.9, and obesity was classified based on a BMI $\geq$ 30 at the time of BM diagnosis. For the purpose of this study, luminal A (LumA) BC was considered when estrogen receptors (ER) were positive (ER^+), progesterone receptors (PR) were positive (PR^+), and human epidermal growth factor receptor (HER2) was negative ($HER2^-$); luminal B $HER2^+$ (LumB $HER2^+$) BC was considered in ER/PR^+ and $HER2^+$ cases; LumB $HER2^-$ BC was considered in ER/PR^+ and $HER2^-$ plus Ki67 > 20% cases; and $HER2^+$ BC was considered in ER/PR^-, $HER2^+$, and triple-negative ER/PR/HER cases. We used the Recursive Partitional Analysis (RPA)[8] and the Graded Prognostic Assessment (GPA)[9] prognostic scales to compare our findings with the literature. The institutional ethics and research committees approved the review of the files.

Statistical Analysis

The mean and standard deviation were used to describe age and the frequency and percentage of the presence or absence of certain variables. The Student *t* test and the Mann-Whitney *U*-test were used to compare continuous variables among groups (BMI $\geq$ 25 vs. < 25), and χ^2 tests were used to assess associations of nonparametric variables. Kaplan-Meier curves with a log-rank test were used to compare bivariable overall survival, and bivariable regression analysis was performed; subsequently, variables with a *P* value < .1 were included in a multivariable Cox regression test. A hazard ratio (HR) with a 95% confidence interval (CI) was used to compare prognostic observations, and a *P* value < .05 was considered statistically significant. We used IBM SPSS Statistics v 25.0 for computations.

Table 1 General Characteristics of the 228 Patients With Brain Metastases From Breast Cancer According to BMI (kg/m^2)

	BMI ≥ 25 N = 108 n (%)	BMI < 25 N = 120 n (%)	*P*
Mean age ± SD, y	51.2 ± 10.8	51.1 ± 10.5	.95
Age, y			
< 50	65 (60%)	78 (65)	
> 50	43 (40)	42 (35)	.4
Subtype			.5
Luminal A	26 (25)	29 (25)	
Luminal B/$HER2^+$	13 (12)	24 (20)	
Luminal B/$HER2^-$	18 (17)	17 (14)	
HER2	23 (22)	23 (20)	
Basal	26 (24)	24 (21)	
GPA			.2
0-1	12 (12)	16 (14)	
1.5-2	38 (36)	33 (28)	
2.5-3	42 (40)	43 (37)	
3.5-4	13 (12)	25 (21)	
RPA			.6
I	5 (5)	8 (7)	
II	67 (62)	68 (57)	
III	36 (33)	43 (36)	
KPS			.3
≥ 70	75 (69)	77 (64%)	
< 70	33 (31)	43 (36)	
Systemic disease	101 (94)	110 (92)	.5
Bone metastases	64 (59)	70 (58)	.8
Liver metastases	38 (35)	40 (33)	.7
Lung metastases	43 (40)	48 (40)	.9
Comorbidity	107 (99)	42 (35)	< .001
Diabetes	24 (22)	16 (13)	.06
Hypertension	31 (29)	26 (22)	.2
Hyperlipidemia	7 (7)	2 (2)	.06

Abbreviations: BMI = body mass index; GPA = Graded Prognostic Assessment; HER2 = human epidermal growth factor receptor 2; KPS = Karnofsky performance score; RPA = Recursive Partitional Analysis.

Results

We analyzed 228 patients with BC and BM. The median age at the time of BC diagnosis was 46 years (range, 25-79 years), and the median age at the time of BM diagnosis was 50 years (range, 30-85 years). The median time from the diagnosis of BC to the diagnosis of BM was 28.9 months (interquartile range, 13.4-70.2 months), and the median follow-up time was 68 months (range, 5-126 months). The median overall survival (MOS) was 12.1 months (95% CI, 10.1-14.0 months), and 108 patients (47%) had a BMI $\geq$ 25, of whom 65 were overweight and 43 were obese. Table 1 describes the characteristics of patients with BM according to the presence or absence of overweight or obesity, and no significant difference was found between groups. Table 2 describes the bivariable survival analysis according to weight and other characteristics; no significant difference in survival was found between patients with a BMI $\geq$ 25 and the BMI < 25 ($P = .3$), overweight ($P = .6$), or obesity ($P = .4$) groups; furthermore, no difference in overall survival was found between the 40 patients who had diabetes and those without diabetes ($P = .5$) (Figure 1). Using the cutoff value of 30 for BMI, the MOS was 10.9 months (95% CI, 7.8-14-2 months) for patients with a BMI $\geq$ 30, and 12.1 months (95% CI, 9.1-15.1 months) for those with BMI < 30 ($P = .5$). A multivariable model was created with BMI as the indicator and adjusted for age, cancer subtype, and KPS; only KPS showed a significant association (HR, 2.3; 95% CI, 1.7-3.1; $P < .001$). A significant difference in survival was observed according to the prognostic scales (RPA and GPA) and the functionality scale (KPS) ($P < .001$).

Table 2 Factors Associated With Survival in Patients With Brain Metastases From Breast Cancer

	Overall Survival, mos (95% CI)	Log-rank *P*	Bivariable Regression Analysis, *P*	Multivariable Hazard Ratio (95% CI)	*P*
Total	12.1 (10.1-14.0)	—	—	—	—
Age, y					
< 50	10.8 (8.4-13.1)				
≥ 50	13.6 (7.3-19.9)	.4	.2	1.3 (0.9-1.7)	.08
BMI ≥ 25	12.6 (9.9-15.1)	.3	.2	0.8 (0.6-1.1)	.16
BMI < 25	11.7 (8.2-15.1)				
Normal weight	11.7 (8.2-15.1)		—	—	
Overweight	12.8 (8.5-17.1)		.6		
Obesity	10.0 (7.7-14.1)	.4	.4		
Diabetes	9.6 (7.1-12.2)	.5	.8	—	
Hypertension	13.3 (9.9-16.6)	.7	.9	—	
Dyslipidemia	17.7 (0-38.4)	.1	.7	—	
Cancer subtype					
LumA	8.7 (5.3-12.2)		.2	1.3 (0.8-2.1)	.1
LumB/HER2$^+$	12.5 (3.8-21.3)		.1	1.3 (0.8-2.0)	.2
LumB/HER2$^-$	10.9 (3.9-17.9)		.5	1.0 (0.6-1.7)	.7
HER2	14.3 (10.3-18.4)		.8	0.8 (0.5-1.4)	.5
Triple negative	8.1 (5.7-10.6)	.026	.15	—	.25
KPS					
≥ 70	17.6 (14.3-20.8)				
< 70	4.8 (3.6-6.1)	< .001	< .001	2.3 (1.7-3.09)	< .001
RPA[a]			—	—	—
I	NR				
II	15.1 (11.3-19.0)				
III	4.9 (3.6-6.3)	< .001			
GPA[a]		< .001	—	—	—
0-1	4.2 (1.4-7.1)				
1.5-2.0	8.8 (6.9-10.8)				
2.5-3	13.0 (8.5-17.5)				
3.5-4	18.6 (11.2-26.0)				

NR = 50% mortality has not been reached.
Abbreviations: BMI = body mass index; GPA = Graded Prognostic Assessment; HER2 = human epidermal growth factor receptor 2; KPS = Karnofsky Performance Score; Lum = luminal; RPA = Recursive Partitional Analysis.
[a]These factors were not included in the multivariable analysis, because they are previously validated prognostic scales.

Discussion

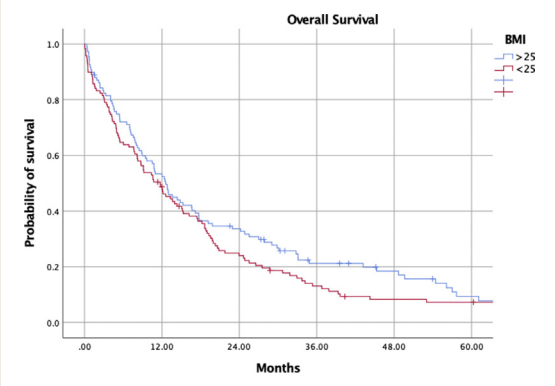
In this series, we found no association between overweight, obesity, or diabetes and survival in patients with BC with BM.

The role of obesity in cancer has been well-studied, but many questions remain, from the specific mechanisms of adipose tissue in carcinogenesis to its impact and clinical significance.[10,11] Obesity could play a role in determining the prognosis of patients with BC, but recent studies have characterized this impact only on the ER$^+$ BC subtype[12]; the reason behind this relationship is still unknown. Multiple factors must be explained regarding the role of obesity and the risk of BM, such as the time of obesity diagnosis (before or after the diagnosis of BC, menopause, BM, etc.). When obesity is diagnosed later in life, it increases the risk of having postmenopausal BC; however, when it is diagnosed during young adulthood, it has been reported to reduce premenopausal BC incidence.[5] Chemotherapy and other medications are usually administered at different doses in patients with a high BMI, which can lead to an altered effectiveness in controlling the disease and might worsen the prognosis.[5,10,11] Furthermore, some studies have reported that a low BMI significantly increases all-cause mortality in patients with BC.[13]

One study found that premenopausal women with elevated BMI had an increased likelihood of developing triple-negative BC[14]; other authors have reported that premenopausal women with an elevated BMI had a decreased risk of developing BC, an increased risk of postmenopausal BC, and a poorer outcome for patients with a history of BC.[15] Although there are many theories about these associations, no conclusive explanations are available at present.

A relevant issue that is often overlooked in research on the relationship between BC and obesity is the standardization of BMI as the principal indicator of obesity. Given the many problems of using BMI, especially poor distinction between body fat and lean

Figure 1 Survival Curve Comparing the Groups of BMI < 25 and BMI > 25



Abbreviation: BMI = body mass index.

mass,[15] and given the relevance of adipose tissue and its mechanisms,[10] BMI should not be further validated as an adequate marker of obesity in BC patients. The use of a poor body composition measure leads to less precise results. For instance, the results from 5 cohort studies differed in pre- or postmenopausal women according to the body composition measure used, with a higher risk of BC observed in premenopausal women stratified by central obesity and a higher risk of BC observed in postmenopausal women stratified by waist-to-hip ratio.[16] Therefore, for a better understanding of obesity in the physiopathology and clinical outcome, a more precise tool should be established to evaluate body composition. However, because BMI is simple to calculate, it remains the standard, and it is beyond the aims of the present work to determine an alternative.

Recently, a large study revealed that the impact of elevated BMI is clear only in ER^+ BC,[2] which is the subtype more commonly found in BC with BM in our population.[17] Although the BM risk is higher in HER2 and triple-negative subtypes[18] as it is in the present study, still 57% were receptor-positive, mainly luminal B type. Furthermore, in our population (Mexican-mestizo), a previous attempt to correlate the prognosis with overweight and obesity in 819 patients with locally advanced cancer showed a poor prognosis in the obese group (HR, 1.79; 95% CI, 1.15-3.2; $P = .012$) but not in the diabetes group[18]; hence, a larger study is needed to ascertain the actual prognosis and pathophysiologic mechanism of overweight/obesity in BC. An important association was observed for the BMI > 25 group. They had a higher frequency of comorbidities than those with a BMI < 25 and had a non-statistically significant increase in the frequency of diabetes, hypertension, and dyslipidemia; a higher frequency of these comorbidities in those with a BMI > 25 is a known association.

Several biases in the present study should be considered, including selection bias, as the included patients were treated at referral centers, and only those treated by the neuro-oncologists were included. To avoid information bias, all data entries were supervised by a neuro-oncologist (B.C.-D., A.G.-A.) and were previously characterized and defined. All statistical analyses were supervised by a specialized epidemiologist (N.R.). The MOS observed in the present study is similar to that reported in the literature; the overall survival ranged from 1 to 55 months, and the MOS ranged from 9 to 15 months.[2,9,19-21] Our MOS results were also similar to those in the original reports of the RPA and GPA (7.1 months and 13.8 months, respectively).[8,9] However, the MOS was different from that reported by studies on the significance of body weight in patients with BM from BC, as fewer patients were previously studied.[3]

Conclusions

Many unanswered questions remain regarding the role of obesity as a prognostic indicator in cancer-affected individuals. We found no relevant association of obesity with overall survival in patients with BM from BC using cutoff values for BMI of 25 (overweight) or 30 (obesity). Thus, further studies are needed to continue evaluating the use of BMI as a prognostic tool in different situations.

Clinical Practice Points

- BC is the second most common source of BM. Up to 30% of patients with BC will develop BM and significantly reduce their survival.
- It has previously been reported that overweight, obesity, and diabetes play a role in the worsening of their prognosis.
- Our significant group of patients analyzed showed no role of neither obesity nor overweight in the prognosis, meaning that we should perfect the way we examine clinically obesity and overweight before using them to define prognosis.

Disclosure

The authors have stated that they have no conflicts of interest.

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