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Body mass index. A predictive factor in the pathological complete response?

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Abstract

Purpose: To evaluate the Body Mass Index (BMI) and the Pathological Complete Response (pCR), survival in patients stage IIB and III who received Neoadjuvant Chemotherapy (NC), Surgery and Radiotherapy at the Mammary Pathology Service of the SOH-IVSS during the period of 2010-2013.

Method: descriptive, retrospective, longitudinal cut, 196 patients received NC stages IIB and III. Results: the median BMI was 28.3 Kg/m^2; 38.3% of our patients had a BMI≥30Kgm^2 (obesity), 70.7% of the obese patients were postmenopausal (p=0.006), the patients with normal weight (96.4%) were more likely to have a ductal carcinoma, 17.3% of obese patients had a non-ductal histological type (p=0.027). The univariate analysis between BMI and pCR showed that the highest percentage of this (pCR) was in patients with normal weight 21.8% when compared with overweight and/or obese patients, not finding statistical significance (p=0.064), however, when combining the overweight/obesity subgroups and compare with the low weight/normal weight group, there was a significant association: 1) with the pCR, that is, lower pCR in patients with a weight>25Kg/m^2 (p=0.022); 2) axillary pCR 60% was in the subgroup of underweight/normal weight patients and non-axillary pCR was greater in the overweight/obese group with 56.2%. (p=0.042). 3) Degree of differentiation (DD) (p=0.04). In the dichotomous logistic regression that relates overweight-obesity with independent variables was observed: higher probability of being obese/overweight if the patient is older than 55 years (OR: 7.22/p<0.001), if it is postmenopausal (OR: 2, 15/p<0.017) and if it was poorly differentiated (OR: 2.58/p<0.04); however, the probability of having a tumor smaller than 5 centimeters (T1-T2) decreases 0.45 times if the patient is obese/overweight (p=0.013). The multivariate regression analysis identified that the BMI: overweight/obesity (OR=0.38/p=0.022) and normal weight/low weight (OR=2.66/p=0.017) are an independent factor for the pCR to the NC. The median follow-up was 42 months (IC-95%: 38.4-44.4 months). Triple-negative patients (TN) with a higher probability of relapse (OR=3.08/p=0.002). There was no statistical association between BMI, recurrence, disease-free survival and overall survival.

Conclusion: In our analysis there was an association between pCR and BMI, in the patients with overweight/ obesity the likelihood of pCR is reduced by 38% and in patients with normal weight, it is more likely to have pCR. The BMI in our series is a relevant clinical factor, predictive for pCR in patients with breast cancer, not affecting survival.

Keywords: breast cancer, body mass index, pathological complete response, obesity

Introduction

Obesity is associated with an increased risk of breast cancer and a worse prognostic after the onset of the disease. However, little is known about the effect of obesity on the efficacy of treatment.[1] The mechanism of this increased risk is not known precisely. Estrogen and perhaps progesterone affect the rate of cell division that causes the proliferation of breast epithelial cells. Proliferating cells are susceptible to genetic errors during DNA replication that, if it is left uncorrected, can ultimately lead to the malignant phenotype.[2]

As has already been described, in postmenopausal women, the main source of estrogen comes from the conversion of the androgen precursor androstenedione in peripheral adipocytes into estrogen.[3,4] as well as being associated with lower levels of Sex hormone binding globulins, (SHBG), which increase the bioavailability of estrogen in obese postmenopausal women.[4-6] therefore, some authors describe a lower incidence of breast cancer in obese premenopausal women and others more daring consider it a protective factor, attributing to frequent anovulatory cycles in these women, which can reduce their overall exposure to estrogen.[4]

Several studies have linked breast cancer with a higher body mass index (BMI), as well as greater tumor size and stage of the disease at the time of diagnosis, however there is variability in the literature when we refer to prognostic; one of the explanations for this thesis is that obesity affects the response to chemotherapy because the conversion to active metabolite and/or the clearance of some cytotoxic drugs can be altered by a higher body weight without a corresponding increase in toxicity.[4,7-10]

While it is true that it is described that obesity measured by BMI increases the plasma levels of estrogen, insulin, and growth factor that somehow promote the growth of metastatic disease, the actual mechanism of its role in prognostic is not yet known; therefore, the purpose of this study is to evaluate the BMI in the pathological response after neoadjuvant chemotherapy (NC) of our patients, and its relationship with survival, in order to determine if this (BMI) is a

predictive factor in the answer, reiterating that obesity constitutes and at the same time is defined as a modifiable risk factor for breast cancer.

Materials and methods

Descriptive, retrospective and longitudinal study of 1362 patients diagnosed with breast cancer between January 2010 and December 2013, treated at the Department of Mammary Pathology of the Hospital Oncology Service of the Venezuelan Institute of Social Security (HOS-IVSS), Ninety-six (196) met the inclusion criteria: 1) female patients with histological and immunohistochemical (HI) diagnosis of breast cancer; over 18 years. 2) Stages IIB and III, tumors were classified according to the parameters of the American Joint Committee on Cancer (AJCC seventh edition).[9] 3) In the medical records register there is the BMI. Patients were categorized as established by the World Health Organization (WHO) 10: low weight (<18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25, 0-29.9 kg/m^2) and obese (≥30 kg/m^2) patients. 4) That they have received NC (standard neoadjuvant chemotherapy treatment line), approved by the Medical Oncology Service of the HOS and surgery in the Service of Mammary Pathology of the HOS. 5) Evaluation of the surgical specimen by specialists of the Pathology Service, using the classification Millare and Page in all the specimens. (The pathological complete response (pCR) of the patients was defined as: ypT0ypN0 or ypTisyN0 and by the Millare and Page classification. The chemotherapy scheme that was most frequently used was: anthracyclines plus cyclophosphamides continuing with taxanes (AC + T, n=165, 84.2%), followed by anthracyclines plus taxanes (AT, n=14, 7.1%); anthracyclines plus cyclophosphamides with or without fluorouracil (CAF/AC, n=8, 4.1%), anthracyclines, cyclophosphamide, fluoracil plus taxanes (CAF+T=5, 2.6%); other schemes four patients (2%); Forty-seven (23.9%) of the fifty-four patients with overexpression of HER 2 received traztuzumab as neoadjuvant accompanied by AC+T or taxanes alone.

Normal and low-weight patients were grouped into a single group, due to the small number of patients in the low-weight category (n=2 1%). As a dichotomous nominal variable, the BMI was classified into two, low/ normal weight vs. overweight/obesity, three, low/normal weight vs. overweight vs. Obese.

In the Medical Oncology service of the HOS, the institutional policy is to dose chemotherapy by actual weight. However, in the majority of patients with overweight and obesity, the Body Surface Area (BS) is rounded to a square of 2.0 m, regardless of its exact measurement, in order to avoid overdose of chemotherapeutics and reduce the increase in toxicity. The data related to the dose of chemotherapy were not available for participants of the study.

Overall and Specific Purposes

To evaluate the body mass index (BMI) and the pathological complete response (pCR), survival in patients stages IIB and III who received neoadjuvant chemotherapy (NC), surgery and radiotherapy at The Mammary Pathology Service of the HOS-IVSS during the period 2010-2013.

Statistic analysis

The median and the standard deviation of the continuous variables were calculated; in the case of nominal variables, their frequencies and percentages were calculated. The contrasts of the variables continuous scale and BMI were analyzed with the one-way analysis of variance test. In the case of nominal variables, Pearson's chi-squared Test was applied. The survival probability of BMI was analyzed by Kaplan-Meier analysis. Survival curves were calculated using the Logarithm-rank Test. To estimate the association between complete response to treatment and relapse, with respect to independent variables, we used the dichotomous logistic regression model. A significant contrast value was considered if $p<0.05$. The data was analyzed with JMP-SAS version 24.

Results

One hundred and ninety-six patients (196) complied the criteria for inclusion at the Service of Breast Pathology of the HOS-IVSS between the years 2010 - 2013. The median age for the diagnosis of the disease was 51 years (with a range between 27 -87 years). 89.8% were reported as infiltrating ductal carcinoma (IDC). Among the prognostic factors the degree of differentiation according to the Scarff Bloom-Richardson scale, the moderately differentiated degree (GII) represented 59.2%. One hundred six patients (54.1%) were T4, one hundred and nineteen patients (60.7%) were positive estrogen receptors; When we refer to the molecular phenotype and its correspondence with the molecular subtype in the sample examined, the Luminal B subtype was the most frequent with eighty-four patients (42.9%), followed by the Triple negatives (TN), with forty and seven (23.9%).

One hundred and sixty-seven patients (85.2%) underwent modified radical mastectomy, followed by partial oncological mastectomy plus axillary dissection (MPO+DA) (14.3%), taking into account that the sample reviewed included breast cancer locally advanced (BCLA) and where the sentinel lymph node selective lymphadenectomy is in study protocol in our center for patients receiving NC. All received neoadjuvant treatment and 87.8% received some kind of adjuvant treatment with chemotherapy and/or hormonal blockade (Table 1).

Table 1 Characteristics of the patients and their Body Mass Index (BMI).

Characterists	Normal	Overweight	Obese	Total	P
N(%)	55 (28,1)	66 (33,7)	75 (38,3)	196	-
Middle(years)	50±11	50±10	53±10	51±10	0,141
Menopausal State					0,006
Premenopausal	31 (56,4)	31 (47,0)	22 (29,3)	84 (42,9)	
Postmenopausal	24 (43,6)	35 (53,0)	53 (70,7)	112 (57,1)	

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(Table 1 continue..)

Histological Type					0,027
Ductal	53 (96,4)	61 (92,4)	62 (82,7)	176 (89,8)	
Others	2 (3,6)	5 (7,6)	13 (17,3)	20 (10,2)	
Tumor size					0,208
T1	1 (1,8)	1 (1,5)	3 (4,0)	5 (2,6)	
T2	14 (25,5)	9 (13,9)	12 (16,0)	35 (17,9)	
T3	18 (32,7)	14 (21,2)	18 (24,0%)	50 (25,5)	
T4	22 (40,0)	42 (63,6)	42 (50,0)	106 (54,1)	
Ganglia					0,727
N0	3 (5,5)	1 (1,5)	3 (4,0)	7 (3,6)	
N1	27 (49,1)	37 (56,1)	32 (42,7)	96 (49,0)	
N2	21 (38,2)	24 (36,4)	34 (45,3)	79 (40,3)	
N3	4 (7,3)	4(6,1)	6 (8,0)	14(7,1)	
Clinical Stage					0,370
IIB	7 (12,7)	5 (7,6)	6 (8,0)	18(9,2)	
IIIA	24 (43,6)	19 (28,8)	23 (30,7)	66(33,7)	
IIIB	20 (36,4)	38 (57,6)	40 (53,3)	98 (50,0)	
IIIC	4 (7,3)	4 (6,1)	6 (8)	14 (7,1)	
Type of surgery					0,759
MRM	47 (85,5)	58 (87,9)	63 (84,0)	168 (85,7)	
MPO+DA	8 (14,5)	8 (12,1)	11 (14,7)	27 (13,8)	
MT	0 (0,0)	0 (0,0)	1 (1,3)	1 (0,5)	

Twelve patients (6.1%) progressed under treatment (NC) were evaluated in the medical oncology service with the respective change in the scheme, however all received surgery after the culmination of the same, the most frequent phenotype found was triple negative with five patients (2.6%) that is, 41.7% of the total of those who progressed.

In the follow-up, 16.8% of our patients presented distant metastases where 6.1% of the whole sample corresponded to TN, that is, 25.5% of this subgroup; 3.6% loco-regional relapse. The median overall survival in the general population was 42 months (IC-95%: 38.4-44.4 months) at the end of follow-up (84 months), the probability of survival was 96.8%; while the median follow-up in the disease-free period was 32.4 months (IC-95%: 26.4-34.4 months) and at the end of the follow-up, the probability of survival was 94.1%.

Relationship between the patient and the tumor characteristics and BMI categories.

The standard BMI was 28.3 Kg/m^2 (with a range between 17-46 Kgm^2); 38.3% of our patients had a BMI≥30Kgm^2 (obesity), in the univariate analysis between the characteristics of the patients and the tumor when related to BMI, we observed that 70.7% of obese patients are postmenopausal, followed by 53% of postmenopausal overweight, the highest percentage of premenopausal patients were normal weight (56.4%) finding statistical association (p=0.006), in the same way when evaluating the histological type there was significance, patients in the low weight/normal weight group (96.4%) were more likely to have an invasive ductal carcinoma compared to overweight (92.4%) and obesity (82.7%), 17.3% of obese patients had a non-ductal histological type

(p=0.027).

The highest percentage of tumors defined as T4 (extension to skin, satellite nodules, orange peel) corresponded to overweight (63.9%) and obese (50%) patients (p=0.208), in the same way the highest percentage of overweight (92.5%) and obese (92%) patients (p=0.370) had stage III tumors. However, the rest of the variables, such as the presence of adenopathies (N), the type of surgery and the tumor size mentioned above, did not show a significant association (Table 2).

Table 2 Relation between BMI, pathological factors and recurrences.

Characteristics	Normal	Overweight	Obese	Total	P
Rpc					0,064
SI	12 (21,8)	7 (10,9)	6 (8,2)	25 (13,0)	
NO	43 (78,2)	57 (89,1)	67 (91,8)	167 (87,0)	
Rpc					0,022
SI	12 (21,8)	13 (9,5)		25 (13,0)	
NO	43 (78,2)	124 (90,5)		167 (87,0)	
Axilar Rpc					0,119
SI	33 (60,0)	27 (42,2)	33 (45,2)	93 (48,4)	
NO	22 (40,0)	37 (57,8)	40 (54,8)	99 (54,6)	
Axilar Rpc					0,042
SI	33 (60)	60(43,8)		93 (48,4)	
NO	22 (40)	77(56,2)		99 (51,69)	
Breast Rpc					0,685
SI	9 (16,4)	11 (16,7)	9 (12)	29 (14,8)	
NO	45 (83,6)	55 (83,3)	66 (88)	167 (85,2)	
Grade of differentiation					0,017
I-II	27 (50,9)	47 (72,3)	52 (73,2)	126 (66,7)	
III	26 (49,1)	18 (27,7)	19 (26,8)	63 (33,3)	
Grade of differentiation					0,004
I-II	27 (50,9)	99(72,8)		126 (66,7)	
III	26 (49,1)	37(27,2)		63 (33,3)	
Molecular Phenotype					0,75
Luminal A	12 (21,8)	12 (18,2)	15 (20,0)	39 (19,9)	
Luminal B	21 (38,2)	27 (40,9)	36 (48,0)	84 (42,9)	
HER 2	7 (12,7)	8 (12,1)	11 (14,7)	26 (13,3)	
Triple negativo	15 (27,3)	19 (28,8)	13 (17,3)	47 (24)	
RE					0,579
Positivo	32 (58,2)	38 (57,6)	49 (65,3)	119 (60,7)	
Negativo	23 (41,8)	28 (42,4)	26 (34,7)	77 (39,3)	
KI67					0,987
< 14	16 (31,4)	20 (32,8)	23 (32,4)	59 (32,2)	
> 14	35 (68,6)	41 (67,2)	48 (67,6)	124 (67,8)	

(Table 2 continue..)

HER2					0,608
Positivo	13 (23,6)	21 (31,8)	21 (28,0)	55 (28,1)	
Negativo	42 (76,4)	45 (68,2)	54 (72,0)	141 (71,9)	
Recurrence					0,333
SI	12 (21,8)	16 (24,2)	11 (14,7)	39 (19,9)	
NO	43 (78,2)	50 (75,8)	64 (85,3)	157 (80,1)	

Relationship between BMI, pathological factors and recurrence.

Twenty-five patients (12.8%) had an pCR, twenty-nine (14.8%) in the breast, obtaining the highest amount of response in the armpit with ninety-three patients (47.4%); It should be noted that four patients did not obtain an answer in the armpit from the total of the sample examined, because adenopathies were not described in the surgical specimen of the axillary dissection.

In the univariate analysis between BMI and pCR we observed that the highest percentage of this was in normal weight patients with 21.8% when compared with overweight and/or obese patients, not finding statistical significance (p=0.064), however, when the overweight/obesity subgroups were combined and compared with the low weight/normweight group, there was a significant association with the pCR, that is, lower pCR in patients with a weight>25Kg/m^2 (p=0.022); this same comparison was made in the axillary pCR obtaining similar results, the highest percentage of response 60% was in the subgroup of patients underweight/normal weight and no axillary pCR was higher in the overweight/obese group with 56.2%. (p=0.042).

The 73.2% of the obese patients obtained the degree of differentiation according to the scale of Scarff Bloom-Richardson, well differentiated GI/GII and the little differentiated (GIII) was more frequent in underweight/normal weight patients with 49.1%, there being statistical significance (p=0.017).

The BMI did not show a significant association with the molecular phenotype, although the highest percentage of obese patients were Luminal B (48%) and HER 2 positive (14.7%), in the same way a subgroup analysis was performed to evaluate the distribution of the BMI category in patients with triple negative breast cancer where there was a trend of a higher percentage of triple negative breast cancers among overweight patients (28.8%) (p =0.750). When was analysed the two subgroups, before mentioned, (overweight/obesity were combined and compared with the normal/low weight group), we observed that the overweight/obese patients had the highest percentage of Luminals B (44.7%) and HER2 (13.5%) and normal weight patients with Luminal A (21.8%) and TN (27.3%) phenotypes (p=0.827).

The rest of the pathological factors studied when relating them to the BMI as the pathologic complete response (pCR) in the breast, estrogen receptors (ER), proliferation index (KI67), there was no statistical association (Table 3).

The highest percentage of local recurrence and/or distance was found in overweight patients in 24.2% (p=0.33). Obese and overweight patients had a higher percentage of tumors that were ER positive and HER 2 (Human Epidermal Growth Factor Receptor 2) positive, respectively, but without statistical association (Table 2).

It should be noted that in this univariate analysis, all the continuous variables were grouped, in addition in two subgroups under weight/normal weight and overweight/obesity, they were reflected in the Table only where there was a significant association such as: pCR, axillary pCR and degree of differentiation (Table 2).

Dichotomous logistic regression that relates overweight-obesity with independent variables.

When performing the multivariate regression analysis, and relating the independent variables (age, degree of differentiation, phenotype, etc.) with overweight/obesity, we observed a higher probability of overweight/obesity if the patient was older than 55 years (Odds Ratio (OR): 7.22/p<0.001), if it is postmenopausal (OR: 2.15/p<0.017) and if it was GIII (OR: 2.58/p<0.04); However, the probability of having a tumor smaller than 5 centimeters (T1-T2) decreases 0.45 times if the patient is overweight/obese (p=0.013). (Table 3).

Table 3 Dichotomous logistic regression that relates overweight-obesity with independent variables.

Variables	OR	IC - 95%		p
All				
Age (> 55 years old)	7,22	3,30	15,83	0,001
Postmenopausal state	2,15	1,14	4,04	0,017
T1-T2 vs T3-T4	0,45	0,24	0,85	0,013
G3 vs G1-G2	2,58	1,34	4,97	0,004
Complete response				

(Table 3 continue..)

Age (> 55years old)	0,45	0,21	1,85	0,005
Postmenopausal state	3,78	1,75	9,87	0,039
Incomplete response				
Edad (≤ 55 años)	5,74	1,79	10,88	0,025
TN presente	4,87	1,87	9,09	0,002
G3 vs G1-G2	3,45	1,30	9,88	0,018

When the independent variables of the patients who had pCR with overweight/obesity were related; we found that the older age 55 years has a probability of 0.45 times (p=0.005) and postmenopausal there are 3.78 times of probability of overweight/obesity (p=0.039). When evaluating all the independent variables of the patients who did not have RPC with overweight/obesity in the multivariate regression analysis we obtained: age <55 years (OR: 5.74/p=0.025), Triple Negative (OR: 4.87/ p=0.002), and GIII (OR: 3.45/p=0.018) we found statistical association for overweight/obesity (Table 3). Analysis of additional subgroups of the molecular phenotype, KI67, RE, RP, etc. where no association was performed (Table 3).

The multivariate regression analysis identified that the BMI (overweight/ obesity) (OR=0.38/p=0.022) is an independent factor for the pCR to the NC, it means that the overweight/obesity reduces the probability of complete response in the 38% and if the patient has normal weight/ low weight, there is 2.66 times the probability of having a pathological complete response (OR=2.66/P=0.017) (Table 4).

Table 4 Logistic regression of the pathological complete response (breast & armpit).

Variables	OR	IC - 95%		p
Age < 55	0,68	0,26	1,80	0,434
Overweight/obesity	0,38	0,16	0,88	0,022
Normal weight	2,66	1,13	6,28	0,017
Postmenopause	0,65	0,28	1,51	0,314
Right breast	0,91	0,39	2,12	0,830
Ductal type	2,72	0,35	6,39	0,535
Estrogen positive	0,56	0,24	1,30	0,173
Progesterone positive	0,63	0,27	1,46	0,274
Her-2	1,24	0,50	3,06	0,644
Ki-67 > 14	1,43	0,53	3,82	0,475
Luminal A	0,53	0,15	1,89	0,474
Luminal B	0,71	0,30	1,69	0,434
Triple negative	1,28	0,50	3,28	0,612
Estadio III	0,72	0,19	2,70	0,908
G3 vs G1-G2	1,39	0,58	3,29	0,460
T1-T2 vs T3-T4	1,30	0,56	3,01	0,544

OR: odds ratio

Recurrence risk/Disease Free Survival (DFS)/Overall Survival OS/ according Body Mass Index.

We can observe in Table No. 5 in the logistic regression analysis that patients under 55 years reduce the probability of relapse in 0.43 times (p=0.045), having positive estrogen, positive progesterone and Luminal B phenotype reduces the probability of relapse in 0.33 times (p=0.002), 0.42 times (p=0.012) and 0.44 times (p=0.025) respectively; unlike TN patients who have a higher probability of relapse (p=0.02). The rest of the variables are not associated.

The overall survival of patients with normal weight did not differ significantly from that of overweight and/or obese patients, despite the fact that the percentage of OS was the lowest in obese patients with 95.1% (CI 95.1-94.3) (p=0.498) (Figure 1).

Regarding the probabilities of disease-free survival again the lowest corresponded to obese patients 95.7% (CI 93.8-96.8), followed by overweight, normal weight, without statistical difference between them; (p=0.516) (Figure 2).

In the present study, obese and overweight patients presented the same type of tumors, clinical stages, molecular phenotype in the presentation compared to normal or underweight patients. While the higher BMI values had a negative effect on the pCR, it did not affect survival

Table 5 Logístic regression of relapse.

Variables	OR	IC - 95%		p
Age> 55	0,43	0,19	1,00	0,045
Overweight/obesity	1,38	0,63	3,03	0,427
Normal weight	0,73	0,33	1,60	0,328
Postmenopause	0,58	0,29	1,14	0,111
Right breast	1,31	0,67	2,59	0,431
Ductal type	0,62	0,22	1,73	0,526
Estrogen positive	0,33	0,16	0,66	0,002
Progesterone positive	0,42	0,21	0,83	0,012
Her-2	0,52	0,22	1,20	0,118
Ki-67 ≥ 14	1,90	0,51	2,34	0,825
Luminal A	0,74	0,30	1,81	0,501
Luminal B	0,44	0,21	0,91	0,025
Triple negative	3,08	1,49	6,38	0,002
Stage III	5,25	0,68	13,28	0,143
G3 vs G1-G2	0,62	0,29	1,33	0,220
T1-T2 vs T3-T4	0,72	0,36	1,43	0,342

OR: odds ratio

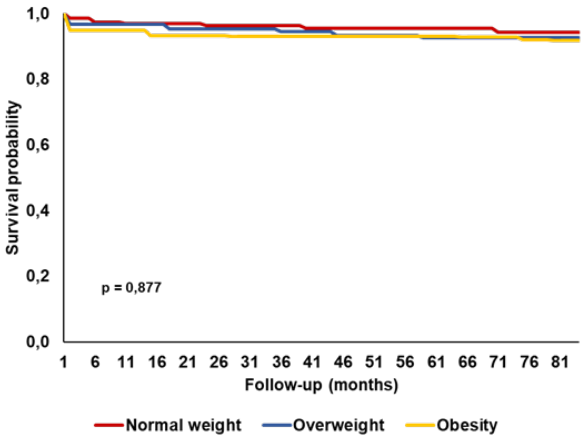

Figure 1: Overall survival according to the BMI.

Log rank test: χ^2 = 1,394 (p = 0,498)

BMI	Md	% of survival	IC-95%	
Normal weight	3,20	97,3	95,3	98,6
Overweight	3,50	96,8	95,0	97,9
Obese	3,60	95,1	94,3	96,8

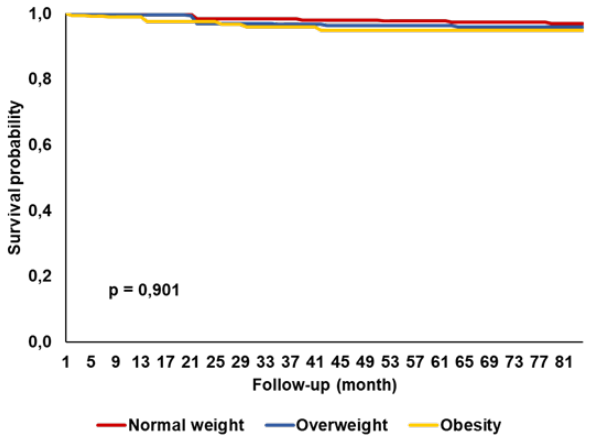

Figure 2 Disease free survival according to the BMI.

Long rank text: χ^2 = 1,325 (p = 0,516)

IMC	Md	% of survival	IC-95%	
Normal weight	2,20	97,3	95,9	98,9
Overweight	2,75	96,1	94,7	97,9
Obese	2,70	95,7	93,8	96,8

Discussion

The relationship between the pCR and the NC has been evaluated in a large number of retrospective, prospective studies and/or trials; for some, this relationship constitutes an independent predictive and predictive factor for survival. However, other authors have not been able to demonstrate a directly proportional relationship between the post-NC pCR and the overall disease-free survival benefit.[11-13] However, time has shown that in certain molecular subtypes with the development of molecular biology, in addiction with a large number of new drugs and/or biological therapies, it would seem to increase not only the overall pCR rate but in some cases survival; therefore, the BMI has been gaining relevance as a predictive factor to the response to the NC, as it will indirectly and positively affect to the survival of the disease.

To date, very few studies have investigated the role of BMI as a predictive factor of response to neoadjuvant chemotherapy (NC), so one of the purposes of our review was to establish this relationship.

Treatment and dosage of chemotherapy

One of the problems posed and no less important in obese patients is the dose of chemotherapy they should receive, authors such as Sawyer et al; Hunter et al; Gurney et al; they have established the possibility that chemotherapeutic agents can diffuse to tissue lipid at higher levels, therefore, the amount of chemotherapeutic agents that need to circulate and diffuse into tumor tissue in obese patients is reduced; remember that the dosing calculations of obese patients are made in relation to the body surface area (BSA).[14-16] However, in the majority of patients with overweight and obesity, the BSA is rounded to a square of 2.0 m, regardless of its exact measurement, in order to avoid overdose of chemotherapeutics and reduce the increase in the toxicity. This, on the other hand, can result in an insufficient treatment dose.[9,15,16] Therefore, independently of the actual BSA of the patients, it is a common practice to limit the drug dose to BSA of $2m^2$ in obese patients in order to prevent any eventual side effects.[17-19] Karatas et al.[19] suggest that combinations of chemotherapy in obese patients should be more aggressive, without dose limitation, and the patient should be individualized to achieve a more favorable outcome.
The subsequent question would be if a reduced dose of chemotherapy in patients with overweight/obesity could have a negative impact on the response of the same, as it is a poorly measurable indicator in most studies, including the current one.

Prognostic factors in the BMI

When the different series, studies, reviews and/or trials are reviewed, we find different results, which for some could be interpreted as contradictory when we refer to the different continuous or categorical variables when relating them to the pCR, the different study populations, diagnostic access precocious, research plans that can influence the variety of results.

One of the prognostic factors described in the various reviews is the status of hormone receptors and it seems logical to think that obese women are prone to have positive hormonal tumors.[9,19-23] This was the case in our study group (65.3%), although it is true that the median age of these patients was 53±10, no statistical association was found; but as mentioned earlier, several studies mention the relationship with the absence of RE in obese patients.

It is described that patients with breast cancer who have a BMI>25kg/m^2 have more frequently adverse prognostic characteristics, such as: negative hormone receptors. 2. TN. 3. More advanced stages of the disease.[19,24-26]

In the cohort study of 1,169 patients with operable breast cancer treated with NC at the MD Anderson Cancer Center of the University of Texas (MDACC), obese patients had the highest percentage of RE negative (46% in obese v 38% in overweight and 36% in normal patients/with low weight, $p<0.01$); similarly, overweight/obese patients were more likely to be TN tumors, which tend to have a higher overall pCR rate to the NC;[9,27] in our review, the highest percentage of negative RE was in overweight patients with 42.4% having no statistical significance.

It is pointed out that patients with a higher body mass index are associated with a more advanced stage of breast cancer at the time of diagnosis in terms of tumor size and/or a more advanced clinical stage when compared with normal or with low weight; this association has been observed in some studies but not in others.[9,28-31] One of the reasons for these claims has been that obesity is a statistically significant determinant of the delay related to the patient in the diagnosis of breast cancer. Obese women are twice as likely to appear before a health professional more than 3 months after they have noticed the symptoms. It is said that obese women are more likely to have large breasts and a breast tumor may be less obvious due to it, leading to a delay in seeking medical attention. Alternatively, the presence of confounding factors such as a greater prevalence of obesity in the lower socioeconomic classes, which is associated with a delay in the diagnosis of breast cancer.[4,32,33]

Litton et al.[9] described that obese patients had stage III tumors (41%), with a predominance of tumors larger than 5 centimeters or with extension to skin when compared to the rest of the subgroups, these variables being statistically significant. In our review, although it is true in the univariate analysis, 63.6% of the overweight patients had tumors classified as T4; there was no statistical association, none of the continuous variables (RE, tumor size, TN) were independent of the pCR in our review.

Relationship of the BMI with the response to the NCAs already described, patients with a higher BMI have a higher incidence of favorable molecular subtypes for the response to neoadjuvant therapy (NT); however, several studies have shown that overweight/obese patients with more aggressive molecular subtypes, the response rate is lower, indicating that the BMI independently and negatively affects response rates, including pCR.[19, 34-36]

In the multivariate analysis conducted by Litton et al.[9] which included 1169 patients, they identified lower rates of pCR for overweight patients but not for obese patients compared to patients with low/normal weight. This negative effect on pCR persisted when patients with overweight and obesity were combined. Cheng et al.[37] obtained the same results; BMI was significantly associated with pCR, considering it as a categorical variable when combining the categories of overweight and obesity ($p=0.019$). However, in the study by Erbes et al.[38] they included

324 patients and an additional meta-analysis on the Current data and relevant studies previously published in the clinical routine, did not show in their work that the BMI categories (continuous, separated into two, three or four groups) had no independent impact on the pCR rate after the NC; but in the pooled analysis of four studies with categorical BMI divided into two subgroups of BMI[39,40] (low/normal weight versus overweight/obese) showed a significant impact of BMI on the pCR rate (p=0.004); in their conclusions Erbes et al.[38] do not establish the BMI as a relevant clinical factor.

Our review has shown that the highest BMI values in breast cancer when analyzing the two overweight/obese subgroups were negatively correlated with the pCR in our population, being statistically significant (OR=0.38/CI 0.16- 0.88/P=0.022), and patients with low-weight/ normal BMI had not only a higher overall pCR rate and axillary pCR in the univariate analysis; but in the logistic regression model, where pCR was more likely (OR=2.66/CI 1.13-6.28/P=0.017). This indicates that the BMI is an independent predictive factor for pCR after the NC.

Recurrence and Survival in relation to the BMI

Prevention of the American Cancer Society, in study II (CPS-II), a prospective mortality study that included 424168 postmenopausal women and 2,852 deaths from breast cancer, found in the 14-year follow-up that mortality rates per Breast cancer increased continuously and substantially with an increasing BMI. The multifactorial relative risk estimates adjusted in this study correspond to approximately 30-50% of deaths from breast cancer among postmenopausal women in the EEUU population. AttribuTable to overweight.[41,42] A cohort study of 3385 women enrolled in protocol B-14 of the National Surgical Breast and Bowel Project (NSABP), a randomized, placebo-controlled trial that evaluated tamoxifen for breast cancer positive to the estrogen receptor (ER), evaluated the risks of recurrence of breast cancer, contralateral breast tumors, other new primary cancers and several end points of mortality, in relation to the body mass index (BMI), finding that the risk of recurrence of breast cancer it was the same in obese women compared to women of low normal weight/weight; for women with negative lymph nodes, breast cancer ER positive, obesity was not associated with a significant increase in the risk of recurrence; however, obesity was associated with an increased risk of contralateral breast cancer, other primary cancers and general mortality.[1]

Again, when reviewing the different series, there are discrepancies between the effect of BMI with recurrence and survival rates, although it is true that several authors associate obesity not only with an advanced tumor stage at the time of diagnosis, but with an increased risk of recurrence and decreased overall survival (OS) in patients with breast cancer.[31,38,43] Other trials and a meta-analysis of molecular subtypes and categorical BMI that includes data from Iwase et al.44 as well as data from other authors revealed that there is no influence of the body mass index on progression-free survival, nor in the survival of specific cáncer.[9,38]

In our review, the probability of recurrence was not associated with BMI, but with the TN phenotype, patients with a tumor with positive hormone receptors had a 33% chance of recurrence; however, in the review by Linton et al.[9] reported that the overall survival of patients with normal weight did not differ significantly from that of overweight patients; however, the survival of obese patients appears to be significantly shorter than the survival of the other two BMI groups.

While it is true that it has been speculated that intrinsic tumor biology contributes to the heterogeneity in disease-free survival of patients with breast cancer who do not obtain an pCR to NC. In fact, the stage, nuclear grade III, negative hormonal receptors, molecular subtype, angiolymphatic invasion, degree of differentiation, are some of the prognostic factors that have been related in the long term with progression-free survival, overall survival in some of the jobs.[9,12,13,38,44,45] Obtaining an pCR at the time of surgery is a well-established substitute marker for overall beneficial survival in different intrinsic subgroups of breast cancer, the evaluation of the pCR predictors has been become an interesting research focus[38]; therefore, the BMI should be considered as a valuable predictor of the poor response to NC in future essays

Conclusions

From our review we can conclude that a BMI≥25 kg/m^2 reduces the likelihood of pCR. It would be interesting to specify if the exact dosage of chemotherapy in obese patients has any influence on the pathological response and whether these reduced doses of treatment in this group of patients has influenced or not, in the various results of the studies, including ours.

The molecular subtype, the degree of differentiation, intratumoral heterogeneity are some of the factors that have been studied in the last five years, as well as the expression profiles of tumor genes, genetic modules related to the immune system, some predictive biomarkers such as liquid biopsy, tumor infiltrating lymphocytes or determination of PD-1 that are still under study to better predict pCR and the results in patients who do not experience the same.

To date, very few studies have investigated the role of BMI as a predictor of response to neoadjuvant chemotherapy, we consider that the BMI is a variable susceptible to evaluation in most centers, without major costs, which can be revealed as Predictive factor of a preliminary nature, while obtaining the results of the multiple biomarkers currently in ongoing clinical essays. Finally, it seems that additional approaches should be considered to investigate the mechanism of influence of BMI on the response to treatment after chemotherapy.

Observations

Our study shows weaknesses such as the following: a) the groups analyzed could present certain population differences among the patients analyzed; b) We could not verify the chemotherapy doses of the patients included in this study and if there was any change during the treatment, either due to weight change and/or toxicity. In the majority of patients with overweight and obesity, the BS is rounded to a square of 2.0 m, regardless of its exact measurement, in order to avoid overdose of chemotherapeutics and reduce the increase in toxicity; however, we must remember that the BMI does not reflect the body composition c) and finally, the data are not generalizable because it is a sample limited to a single hospital, although our hospital is considered a national reference for the treatment of carcinoma of the breast.

Conflicts of interest

The author(s) indicated no potential conflicts of interest.

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