Sentinel Node Biopsy after Neoadjuvant Chemotherapy in Breast Cancer: Real Life Results

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Biópsia de Linfonodo Sentinela após Quimioterapia Neoadjuvante em Câncer de Mama: Resultados da Vida Real

Biopsia del Ganglio Centinela tras Quimioterapia Neoadyuvante en Cáncer de Mama: Resultados de la Vida Real

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ABSTRACT

Introduction: Breast cancer (BC) is the most common cancer among women. Neoadjuvant chemotherapy (NAC) aims to improve surgical conditions in patients with locally advanced BC. **Objective**: Compare demographic, clinical and treatment characteristics of women undergoing NAC for BC treatment according to axillary lymphadenectomy (AL) or sentinel lymph node biopsy (SLNB) and analyze factors associated with indication of SLNB in a real-life scenario. **Method**: Retrospective cohort study of women with BC and indication for NAC. Demographic, clinical, tumor and treatment variations were obtained. Simple and multiple logistic regression was performed to evaluate the independent factors associated with SLNB indication. **Results:** 918 patients were included, of which 17.5% underwent SLNB and 11.4%, SLNB followed by AL. Women in stage III were 95% less likely to undergo SLNB (OR = 0.05; 95% CI: 0.01-0.17; $p < 0.001$) compared to those in stage I. Those submitted to mastectomy had 90% less odds of submitting to SLNB than those submitted to conservative surgery (95% CI: 0.06-0.17; p < 0.001). Considering NAC responses, cases without response or with disease progression had a 55% lower chance of undergoing SLNB compared to those who had a complete response (OR = 0.45; 95% CI: 0.24-0.82; $p = 0.009$). **Conclusion**: SLNB was performed in 29% of patients after NAC. Patients who had a more advanced clinical stage of the disease, with a worse response to NAC and those who underwent mastectomies were less likely to undergo SLNB.

Key words: Drug Therapy; Breast Neoplasms/surgery; Lymph Node Excision; Sentinel Lymph Node Biopsy; Demography.

RESUMO

Introdução: O câncer de mama (CM) é o mais comum entre as mulheres. A quimioterapia neoadjuvante (QTNEO) visa melhorar as condições cirúrgicas em pacientes com CM localmente avançado. **Objetivo:** Comparar as características demográficas, clínicas e de tratamento de mulheres submetidas à QTNEO para tratamento de CM de acordo com a linfadenectomia axilar (LA) ou biópsia de linfonodo sentinela (BLS) e analisar os fatores associados à indicação de BLS em um cenário da vida real. **Método:** Estudo de coorte retrospectivo em mulheres com CM e indicação de QTNEO. Foram obtidas variáveis demográficas, clínicas, tumorais e de tratamento. Foi realizada regressão logística simples e múltipla para avaliar os fatores independentes associados à indicação de BLS. **Resultados**: Foram incluídas 918 pacientes, das quais 17,5% foram submetidas à BLS e 11,4% à BLS seguida de LA. As mulheres em estádio III tiveram 95% menos probabilidade de serem submetidas à BLS (OR = 0,05; IC 95%: 0,01-0,17; $p < 0,001$) em comparação com aquelas no estádio I. As submetidas à mastectomia apresentaram 90% menor chance de realizar BLS do que aquelas com cirurgia conservadora (IC95%: 0,06-0,17; $p < 0,001$). Considerando as respostas da QTNEO, os casos sem resposta ou com progressão da doença apresentaram chance 55% menor de serem submetidos à BLS em comparação às que apresentaram resposta total (OR = 0,45; IC 95%: 0,24-0,82; p = 0,009). **Conclusão**: A BLS foi realizada em 29% das pacientes após QTNEO. Pacientes que apresentavam estágio clínico mais avançado da doença e pior resposta à QTNEO e as que foram submetidas a mastectomias tiveram menor probabilidade de serem submetidas à BLS.

Palavras-chave: Tratamento Farmacológico; Neoplasias da Mama/cirurgia; Excisão de Linfonodo; Biópsia de Linfonodo Sentinela; Demografia

RESUMEN

Introducción: El cáncer de mama (CM) es el más común entre las mujeres. La quimioterapia neoadyuvante (QTNEO) busca mejorar a las condiciones quirúrgicas en pacientes con cáncer de mama localmente avanzado. **Objetivo:** Comparar las características demográficas, clínicas y de tratamiento de las mujeres sometidas a QTNEO para el tratamiento de CM según si se trata de linfadenectomía axilar (LA) o biopsia del ganglio linfático centinela (BGC) y analizar los factores asociados con la indicación de SLNB en un escenario de la vida real. **Método**: Estudio de cohorte retrospectivo de mujeres con CM e indicación de QTNEO. Se obtuvieron diversas variables demográficas, clínicas, tumorales y de tratamiento. Se realizó regresión logística simple y múltiple para evaluar los factores independientes asociados con la indicación de BGC. **Resultados**: Se incluyeron 918 pacientes, de las cuales al 17,5% se le realizó BGC y al 11,4% se le realizó BGC seguida de LA. Las mujeres en el estadio III tuvieron un 95% menos de probabilidades de someterse a una BGC (OR = 0,05; IC del 95%: 0,01-0,17; $p < 0,001$) en comparación con aquellas en el estadio I. Las que se sometieron a una mastectomía tuvieron un 90% menos de posibilidades de someterse a una BGC que aquellas con cirugía conservadora (IC 95%: 0,06-0,17; $p < 0,001$). Considerando las respuestas de QTNEO, los casos sin respuesta o con avance de la enfermedad presentan un 55% menos de probabilidad de ser remitidos a la BGC en comparación con aquellos que presentan respuesta total (OR = 0,45; IC 95%: 0,24- 0,82; $p = 0,009$). **Conclusión:** La BLS se realizó en el 29% de los pacientes después de QTNEO. Las pacientes que tenían un estadio clínico más avanzado de la enfermedad, con peor respuesta a QTNEO y aquellas que se sometieron a mastectomías tenían menos probabilidades de someterse a BGC.

Palabras clave: Quimioterapia; Neoplasias de la Mama/cirugía; Escisión del Ganglio Linfático; Biopsia del ganglio centinela; Demografía.

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INTRODUCTION

Breast cancer (BC) is the most common cancer among women. Its incidence corresponded to 11.6% of all malignancies in 2022 and to 23.8% of all cancer cases in women, also being the main cause of death by cancer in the female population[1]. In Brazil, BC is also the most common cancer type among women, with 77,610 new cases estimated for each year of the triennium 2022-2024 triennium[2].

Throughout history, BC treatment has undergone numerous transformations, and a better understanding of the pathophysiology of the disease has been reached. Treatment evolved from a predominantly surgical approach, supported by the theory of centrifugal disease dissemination, whose main objective was locoregional control, to multidisciplinary management and the introduction of systemic therapy, resulting in significant survival improvements[3].

Chemotherapy is adopted within the systemic approach of the disease and, when performed prior to surgery (neoadjuvant), aims to achieve better conditions for surgical breast resection in patients with locally advanced and inoperable BC. However, in the last decade, neoadjuvant chemotherapy (NAC) has become relevant for other purposes, as clinical studies on the effectiveness of antineoplastic *in vivo* agents, evaluation of predictive and prognostic biomarkers in tumor responses and conservative surgical treatments with better aesthetic results, not only in cases of advanced carcinoma but also in early breast carcinomas. Another benefit more recently observed of neoadjuvancy is the possibility of adding new drugs to the adjuvant if no pathological response occurs during the first systemic approach[3-8].

Classic surgery consists in axillary lymphadenectomy (AL) as axillary approach after NAC, and studies attempting to establish the validity of sentinel lymph node biopsy (SLNB) in the prediction of axillary status have shown this to be a reliable method with a high potential for incorporation into clinical practice. This is, however, still a controversial topic, as studies have reported divergent results[7,9-13].

In this context, this study aims to compare demographic, clinical and treatment characteristics of women undergoing NAC for BC treatment according to the axillary approach and analyze factors associated with SLNB indication in a real-life scenario.

METHOD

Cohort study with retrospective data collection was conducted in women diagnosed with BC with SLNB from January 2013 to December 2015, in a single BC reference treatment institution *Hospital do Câncer III* of the National Cancer Institute (HC-III/INCA). The exclusion criteria were: bilateral BC, inflammatory breast carcinoma, non-epithelial tumors, occult breast carcinoma, pregnant women, history of previous cancer, cancer treatment prior to enrollment at the hospital, contraindication for surgical treatment after neoadjuvant chemotherapy, evolution of systemic disease during NAC, following other chemotherapy protocols (without adriamycin and cyclophosphamide or taxane) and SLNB prior to NAC.

Data were collected from physical and electronic charts with an instrument created specifically for this purpose. The following groups of variables were collected:

Demographic: age at the date of hospital admission, race/skin color according to the first medical record, marital status reported in the date of surgery, educational level (years of study) and main occupation until diagnosis.

Clinical: alcoholism and smoking according to the medical chart, comorbidity by the Charlson comorbidity index (CCI) with total score ranging from 0 to 37 points and the results stratified as the absence (score 0) and presence (score ≥1) of comorbidities, body mass index during the first weight and height assessment performed by the Nutrition Service categorized as low weight (<18.5), normal weight (18.5-24.9), pre-obesity (25.0-29 , 9) and obesity (≥ 30.0).

Tumoral: tumor side as described in the histopathological report, clinical classification for tumor size (cT) and axillary lymph node (cN), clinical staging (TNM) classified as I, IIA, IIB, IIIA, IIIB and III C, histological type and grade according to the histopathological report of the diagnostic biopsy, expression of the HER2 receptor, expression of estrogen receptors (RE), progesterone (RP) and Ki-67 cell proliferation index obtained from the biopsy histopathological report or surgical specimen. Based on these information, tumors were classified by molecular subtype into luminal A (RE + and/or RP+, HER2-), luminal B (RE+ and/or RP+ and HER2+ or high ki-67 and HER2-); overexpression of HER2 (RE-, RP- and HER2 +); and basal-like or triple-negative (RE-, RP- and HER2-).

Neoadjuvant cancer treatment: chemotherapy treatment scheme, other neoadjuvant treatments (radiotherapy, hormone therapy and Herceptin®) and clinical hospitalization during neoadjuvant treatment. The time between the end of the neoadjuvant treatment and the surgery was also noted.

Response to NAC: comparisons between the clinical tumor (cT) and the histopathological (pT) size and classification of the clinical (cN) and pathological (pN) lymph nodes was performed to assess responses to NAC. A total response was

considered when pT and pN were equal to 0. The remaining cases were classified as partial response (when cT and cN maintained or decreased their classification but did not reach 0) or disease progression (when an increase in the cT and cN classification was observed).

Surgical and adjuvant treatment: type of breast surgery (mastectomy or conservative surgery), type of axillary surgery (AL, SLNB or both); AL level as described in the surgical report (levels I, II or III), number of lymph nodes removed in each axillary approach, according to histopathological report; status of axillary lymph nodes in each axillary approach according to histopathological report; and adjuvant treatment (chemotherapy, radiotherapy, hormone therapy and target therapy).

A descriptive analysis of the study population was performed, utilizing central tendency (mean) and dispersion (standard deviation) measures for continuous variables and absolute and relative frequency distributions for categorical variables. The chi-square test compared the frequency distribution of the demographic and clinical characteristics obtained according to the axillary approach (SLNB with or without AL versus AL). The Z test was applied in order to identify differences between categories for statistically significant differences ($p < 0.05$) and variables with three or more categories. A simple logistic regression was implemented using the crude odds ratio (OR) to assess independent factors associated with indication for SLNB. Variables with $p < 0.20$ were selected for the multiple model, which was constructed using the Stepwise Forward method. Statistically significant factors were maintained in the final model ($p < 0.05$). The Statistical Package for the Social Sciences (SPSS)[14] version 23.0 software was used for all statistical analyses.

INCA's Research Ethics Committee (CEP) approved the study, report 166838 CAAE (submission for ethical review), number 06794512.3.0000.5274, in compliance with Directive 466/2012[15] of the National Health Council.

RESULTS

During the study period, 3,211 women were enrolled for BC treatment at the HC III/INCA. Of these, 11.9% were at clinical staging IV and 53.7% were not submitted to NAC. The physical charts of the 1,106 eligible women were reviewed, and 188 women were excluded for not meeting the eligibility criteria. The final number of patients evaluated herein comprised 918 women treated with NAC, 161 (17.5%) of whom underwent SLNB, 105 (11.4%), SLNB followed by AL and 652 (71.0%), AL alone (Figure 1).

The patients had a mean age of 51.58 years (SD ± 11.46), 15.4% categorized as young (<40 years old) and 13.2%, as older patients (≥65 years old). Most of them reported they were living without spouse (58.7%), completed more than eight years of education (56.8%), claimed they were non-white (65.5%) and were more frequently submitted to SLNB (72.2%) compared to white women (27.8%) ($p = 0.009$).

Statistically significant difference of 38.1% and 61.9%, respectively among retired, pensioner, housewife and unemployed patients and those currently working who submitted to SLNB was found ($p = 0.013$) (Table 1).

Regarding comorbidities, 372 (40.5%) of the patients presented systemic arterial hypertension and 106 (11.5%), diabetes. When applying the CCI, 86.7% had no comorbidities. A higher SLNB frequency was observed in women without systemic arterial hypertension ($p = 0.041$) and without diabetes ($p = 0.047$) (Table 1).

Tumor characteristics according to the applied axillary approach are presented in Table 2. A higher SLNB frequency was observed in patients at cT1 and cT2, while AL was performed more frequently in patients at cT4 ($p < 0.001$). Regarding clinical lymph node involvement, 65.8% of the patients at cN0 underwent SLNB, while the others more frequently underwent AL ($p < 0.001$).

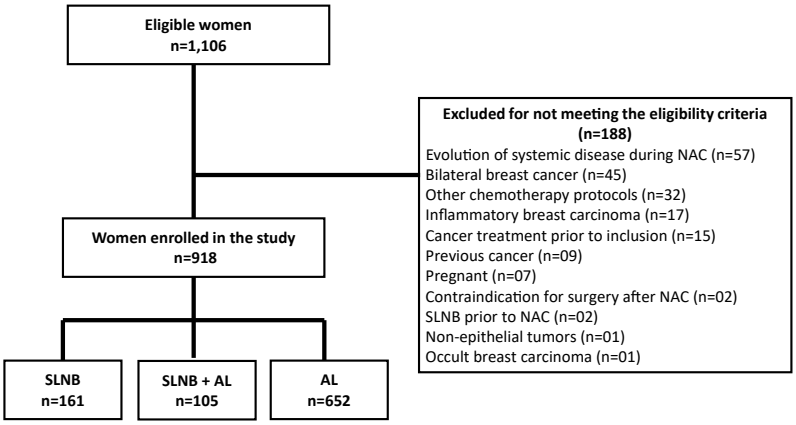

Figure 1. Flowchart of identification of study patients

Captions: NAC = neoadjuvant chemotherapy; AL = lymphadenectomy; SLNB = sentinel lymph node biopsy.

Table 1. Demographic, clinical and treatment characteristics of women undergoing neoadjuvant chemotherapy (NAC) for breast cancer (BC) treatment according to the axillary approach (n=918)

Variables	Total N (%)	Axillary approach		p value**
		AL (n=652) N (%)*	SLNB (n=266) N (%)*	
Age (years)				
Mean (SD)	51.58 (11.46)	51.92 (11.30)	50.74 (11.83)	0.157
Age group				
< 40 years	141 (15.4)	90 (13.8)	51 (19.2)	
40 - 64 years	656 (71.5)	475 (72.9)	181 (68.0)	0.122
≥ 65 years	121 (13.2)	87 (13.3)	34 (12.8)	
Race/skin color				
White	313 (34.1)	239 (36.9)	74 (27.8)	0.009
Non-white	601 (65.5)	409 (63.1)	192 (72.2)	
Missing	04 (0.4)			
Marital status				
With spouse	370 (40.3)	254 (39.4)	116 (43.8)	0.227
Without spouse	539 (58.7)	390 (60.6)	149 (56.2)	
Missing	09 (1.0)			
Years of study				
< 8 years of study	382 (41.6)	276 (43.1)	106 (40.3)	0.436
≥ 8 years of study	521 (56.8)	364 (56.9)	157 (59.7)	
Missing	15 (1.6)			
Main occupation				
No current work relationship	280 (30.5)	206 (48.9)	74 (38.1)	0.013
Currently working	335 (36.5)	215 (51.1)	120 (61.9)	
Missing	303 (33.0)			
Alcohol use				
No	661 (72.0)	466 (76.4)	195 (76.8)	
Yes (occasional or frequent)	188 (20.5)	135 (22.1)	53 (20.9)	0.623
Ex-user	15 (1.6)	09 (1.5)	06 (2.4)	
Missing	54 (5.9)			
Smoker				
No	616 (67.1)	442 (72.2)	174 (68.0)	
Yes (occasional or frequent)	252 (29.0)	170 (27.8)	82 (32.0)	0.208
Missing	50 (5.4)			
Systemic arterial hypertension				
No	546 (59.5)	374 (57.4)	172 (64.7)	0.041
Yes	372 (40.5)	278 (42.6)	95 (35.3)	
Diabetes				
No	812 (88.5)	568 (87.1)	244 (91.70)	0.047
Yes	106 (11.5)	84 (12.9)	22 (8.3)	
Charlson comorbidity index				
0 (absence)	796 (86.7)	557 (85.7)	239 (89.8)	0.090
≥1 (presence)	120 (13.1)	93 (14.3)	27 (10.2)	
Missing	02 (0.2)			
Body mass index				
Mean (SD)	28.84 (5.61)	28.92 (5.63)	28.65 (5.60)	0.523
Nutritional status				
Low or normal weight (<24.9)	242 (26.4)	172 (26.5)	70 (26.3)	
Pre-obesity (25.0 to 29.9)	341 (37.1)	237 (36.5)	104 (39.1)	0.713
Obesity (≥30)	333 (36.3)	241 (37.1)	92 (34.6)	
Missing	02 (0.2)			

Captions: SD = standard deviation; AL = axillary lymphadenectomy; SLNB = sentinel lymph node biopsy.
* Percentage in columns; ** Calculated with known values.

Table 2. Tumoral characteristics of women undergoing neoadjuvant chemotherapy (NAC) for breast cancer (BC) treatment according to the axillary approach (n=918)

Variables	Total N (%)	Axillary approach		*p* value**	Z Test ***
		AL (n=652) (A) N (%)*	SLNB (n=266) (B) N (%)*		
Tumor side					
Right	442 (48.1)	309 (47.4)	133 (50.0)	0.473	
Left	476 (51.9)	343 (52.6)	133 (50.0)		
Tumor size (cT)					
T1	27 (2.9)	10 (1.5)	17 (6.4)	<0.001	A<B
T2	316 (34.5)	161 (24.7)	155 (58.3)		A<B
T3	274 (29.8)	186 (28.5)	88 (33.1)		A=B
T4	301 (32.8)	295 (45.2)	06 (2.3)		A>B
Axillary lymph node (cN)					
N0	392 (42.7)	217 (33.3)	175 (65.8)	<0.001	A<B
N1	390 (42.5)	303 (46.5)	87 (32.7)		A>B
N2 e N3	136 (14.8)	132 (20.2)	04 (1.5)		A>B
Clinical staging (TNM)					
I	21 (2.3)	05 (0.8)	16 (6.0)	<0.001	A<B
II A	187 (20.4)	80 (12.3)	107 (40.2)		A<B
II B	219 (23.9)	118 (18.1)	101 (38.0)		A<B
III A	189 (20.6)	153 (23.5)	36 (13.5)		A>B
III B	291 (31.7)	285 (43.7)	06 (2.3)		A>B
III C	11 (1.2)	11 (1.7)	0		A>B
Histological type					
IDC-NST	841 (91.6)	598 (71.1)	243 (28.9)	0.857	
Others	77 (8.4)	54 (70.1)	23 (29.9)		
Histological grade					
Grade 1	52 (5.7)	35 (67.3)	17 (32.7)	0.395	
Grade 2	571 (62.2)	397 (69.5)	174 (30.5)		
Grade 3	263 (28.6)	194 (73.8)	69 (26.2)		
Missing	32 (3.5)				
Estrogen receptors					
Negative	261 (28.4)	192 (29.4)	69 (25.9)	0.285	
Positive	657 (71.6)	460 (70.6)	197 (74.1)		
Progesterone receptors					
Negative	361 (39.3)	254 (39.0)	107 (40.2)	0.721	
Positive	557 (60.7)	398 (61.0)	159 (59.8)		
Overexpression of HER2					
Negative	691 (75.3)	498 (76.5)	193 (73.1)	0.280	
Positive	224 (24.4)	153 (23.5)	71 (26.9)		
Missing	03 (0.3)				
Ki-67 (classification)					
Low (<14%)	199 (21.7)	139 (22.5)	60 (23.4)	0.762	
High (≥14%)	675 (73.5)	479 (77.5)	196 (76.6)		
Missing	44 (4.8)				
Molecular subtype					
Luminal A	163 (17.8)	116 (18.4)	47 (18.1)	0.678	
Luminal B	479 (52.2)	332 (52.7)	147 (56.8)		
Overexpression of HER2	72 (7.8)	53 (8.4)	19 (7.3)		
Basal-like or triple-negative	175 (19.1)	129 (20.5)	46 (17.8)		
Missing	29 (3.2)				

Captions: AL= axillary lymphadenectomy; SLNB = sentinel lymph node biopsy; IDC-NST = Invasive ductal carcinoma no specific type.

*Percentage in columns; **Calculated with known values; ***Only calculated for p <0.05 and for variables with three or more categories.

The molecular subtypes luminal A (17.8%) and luminal B (52.2%) were found for the majority of the patients, with no difference of SLNB frequency.

The average time between the last NAC cycle and surgery was 70 days (± 39) and was longer for patients submitted to SLNB (p <0.001). For breast surgery, SLNB was more frequent in women who underwent mastectomies (53.0%) (p <0.001). In 16 (1.6%) of the cases, a surgical re-approach was required to locally control the disease, and patients have been previously submitted to SLNB in 11 of these cases, (p <0.001). Adjuvant treatment was applied in 96.8% of the patients with chemotherapy (0.3%), trastuzumab (23.0%), radiation therapy (89.5%) and hormone therapy (71.4%). No statistically significant differences between adjuvant treatment and the axillary approach were observed (Table 3).

Table 4 describes the results of the crude and adjusted analyzes. Clinical stage, NAC response and type of surgery were associated with SLNB.

In the adjusted model, as more advanced the clinical stage, less were the odds of undergoing SLNB. In comparison with patients in stage I, women in stage III had 95% lower odds of undergoing SLNB (OR= 0.05 95% CI 0.01-0.17; p < 0.001). Women who underwent mastectomies had 90% lower odds of undergoing SLNB compared to those who underwent conservative surgeries (95% CI 0.06-0.17; p <0.001). Cases without responses to NAC or with disease progression had 55% lower odds of undergoing SLNB compared to those with a total response (OR = 0.45 95% CI 0.24-0.82; p = 0.009) (Table 4).

DISCUSSION

A total of 918 women were analyzed in this observational study with real-life results, where 29% were submitted to SLNB after NAC to treat BC. Those at a more advanced clinical stage with worse response to NAC, and those who underwent mastectomies were less likely to undergo SLNB.

Table 3. Breast cancer treatment of women undergoing neoadjuvant chemotherapy (NAC) according to the axillary approach (n=918)

Variables	Total N (%)	Axillary approach		p value**
		AL (n=652) N (%)*	SLNB (n=266) N (%)*	
Time between the last NAC cycle and surgery (days)				
Mean (SD)	70.7 (39.1)	63.0 (36.7)	89.5 (38.5)	<0.001
Breast surgery				
Mastectomy[a]	759 (82.7)	618 (94.8)	141 (53.0)	<0.001
Conservative surgery	159 (17.3)	34 (5.2)	125 (47.0)	
Surgical re-approach				
No	902 (98.4)	647 (99.2)	255 (95.9)	<0.001
Yes	16 (1.6)	05 (0.8)	11 (4.1)	
Adjuvant treatment				
No	29 (3.2)	25 (3.8)	04 (1.5)	0.067
Yes	889 (96.8)	627 (96.2)	262 (98.5)	
Adjuvant chemotherapy				
No	915 (99.7)	649 (99.5)	266 (100)	0.268
Yes	03 (0.3)	03 (0.5)	0	
Adjuvant Herceptin®				
No	707 (77.0)	509 (78.1)	198 (74.4)	0.235
Yes	211 (23.0)	143 (21.9)	68 (25.6)	
Adjuvant Radiotherapy				
No	96 (10.5)	61 (9.4)	33 (12.4)	0.167
Yes	822 (89.5)	591 (90.6)	233 (87.6)	
Adjuvant Hormone Therapy				
No	263 (28.6)	194 (29.8)	69 (25.9)	0.246
Yes	655 (71.4)	458 (70.2)	197 (74.1)	

Captions: NAC = neoadjuvant chemotherapy; SD = Standard deviation; AL= axillary lymphadenectomy; SLNB = sentinel lymph node biopsy.

* Percentage in columns; ** Calculated with known values.

Table 4. Multiple logistic regression to assess factors associated with indication for SLNB and independent variables (n=918)

Variables	Univariate		Multiple (adjusted)	
	Crude OR (95% CI)	*p* value*	Adjusted OR (95% CI)	*p* value*
Age (years)				
Continuous	0.99 (0.98 – 1.00)	0.157	---	---
Race/skin color				
White	Reference	0.009	---	---
Non-white	1.52 (1.11 – 2.07)			
Main occupation				
No current work relationship	Reference	0.013	---	---
Currently working	1.55 (1.10 – 2.20)			
Systemic arterial hypertension				
No	Reference	0.041	---	---
Yes	0.73 (0.55 – 0.99)			
Diabetes				
No	Reference	0.047	---	---
Yes	0.61 (0.37 – 0.99)			
Charlson comorbidity index				
0 (absence)	Reference	0.090	---	---
≥1 (presence)	0.68 (0.43 – 1.07))			
Tumor size (cT)				
T1	Reference			
T2	0.57 (0.25 – 1.27)	0.170	---	---
T3	0.28 (0.12 – 0.63)	0.002		
T4	0.01 (0.00 – 0.04)	<0.001		
Axillary lymph node (cN)				
N0	Reference			
N1	0.36 (0.26 – 4.87)	<0.001	---	---
N2 e N3	0.04 (0.01 – 0.10)	<0.001		
Clinical stage (TNM)				
I	Reference		Reference	
II	0.33 (0.12 – 0.91)	0.033	0.46 (0.14 – 1.52)	0.204
III	0.03 (0.01 – 0.08)	<0.001	0.05 (0.01 – 0.17)	<0.001
Adjuvant Herceptin®				
No	Reference	0.067	---	---
Yes	1.37 (0.98 – 1.91)			
NAC response				
Complete	Reference		Reference	
Partial	0.38 (0.25 – 0.57)	<0.001	0.60 (0.35 – 1.01)	0.056
No response or progression	0.48 (0.30 – 0.76)	0.002	0.45 (0.24 – 0.82)	0.009
Breast surgery				
Mastectomy	Reference	<0.001	Reference	<0.001
Conservative surgery	0.06 (0.04 – 0.09)		0.10 (0.06 – 0.17)	

Captions: OR= odds ratio; NAC = neoadjuvant chemotherapy; CI = confidence interval.

The studied population displayed a mean age of 51.58 years old, similar to other series of BC patients who underwent NAC[16-18]. The younger age in patients undergoing NAC can be partly explained by the fact that more aggressive tumors occur at younger ages and are associated with a greater indication for this type of treatment[16,17].

Most women claimed their skin color was Brown (47.7%), followed by White (34.1%) and Black (17.5%). The highest percentage of Brown women, when considered as a socioeconomic level proxy, may reflect greater difficulty to access medical care, resulting in late diagnoses and more advanced cancer stage. The relationship between access difficulties and worse health outcomes is already well established in general, and malignant breast neoplasms seem to follow this rule. Therefore, it is plausible to think of skin color as not associated, in general, to more advanced BC stages, but instead, as of an indicator of differential health care access[19-23]. It is important to note that this data was self-reported by the study participants, an obstacle to characterize this variable, further to the high Brazilian population miscegenation.

The molecular cancer subtypes luminal B corresponded to 52.2% of the cases, followed by triple-negative with 19.1%, luminal A with 17.8% and HER2 with 7.8%. In Brazil, the most frequent subtype is luminal B[18,24,25]. However, different incidences among the five Brazilian regions have been noticed. In the Southeast region, this type corresponds to 39.5 % of cases, followed by luminal A with 28.8%, triple-negative, 14.0% and HER2, 7.9%[26].

In other populations submitted to NAC, the luminal molecular subtype B has been reported as the most frequent[27,28]. In a cohort of 601 patients with the objective of describing the immunohistochemical profile of BC, Cintra et al.[24] observed that most patients in stage III presented luminal subtype B, with 53.1%, followed by triple-negative, with 35.9% of all the cases. Luminal subtype A is a tumor subtype associated with lower aggression, earlier stage tumors and low response to NAC, as well as higher false-negative results in SLNB, which could explain the lower frequency in patients undergoing NAC[24,29]. Thus, it is understood that the incidence of molecular subtypes in the population assessed herein is influenced by profiles displaying greater tumor aggressiveness and, consequently, higher indication for NAC.

The initial clinical size of the tumor (cT) and the axillary status (cN) in the crude analysis were associated with an axillary approach indication. The clinical axillary evaluation (cN) is also used to indicate SLNB before chemotherapy, considering that anatomical BC staging is clinical[30]. In the present study, this evaluation was conducted prior to NAC and the absence of clinical axillary involvement (cN0) was observed in 65.8% of patients with an SLNB indication after NAC. In cases where the axillary nodes are clinically negative (cN0), they remain as such most of the time after NAC, 62.0% of the patients classified as cN0 were negative by the histopathological examination (ypN0), while 38.0% displayed a positive result (ypN1). Galimberti et al.[31] reported that of 249 patients considered cN0 prior to NAC, 36.9% of the anatomopathological results were positive (ypN1). In a study conducted with a secondary database including 32,036 American women undergoing NAC, those who underwent SLNB displayed lower cN and greater pathological complete response (pCR) compared to those submitted to AL[17] (66.5% *versus* 33.1%, respectively).

Clinical axillary assessments after NAC was not analyzed herein, which limits the accuracy of the exams, although the specialized literature reports low accuracy. The Fine-Needle Aspiration Cytology (FNAC) study demonstrated that the clinical axillary negative predictive value after NAC was of 38%, the rate of false-negative results was 82% and the positive predictive value was 89%, concluding that the accuracy of the physical axillary examination after NAC is 45%[32].

In addition, in patients with SLNB indication, the axillary nodes were classified as clinically positive (cN1/2/3) in 34.2% of the cases. Pathological anatomy evaluations identified positive armpits in most of the patients (62.9%), with 37.1% negative. The literature demonstrates that the conversion of positive (cN1) to negative (ypN0) axillary nodes is 28%[32]. This may indicate that, in addition to axillary node response, an overestimation of the axillary clinical evaluation may have occurred in the current analysis.

Mastectomy was the most frequent surgery in 82.7% of the cases. Even in patients with indication for SLNB, 53.0% of the cases were submitted to mastectomy, compatible with the complete response rate of 13.5% and partial response of 63.6%. The literature demonstrates that, despite the increased response to NAC, it did not reflect into an increase in conservative surgeries as it would be expected[33]. While response rates around 30% to 40% were observed for some subtypes, the rate of reduction in mastectomies in some series is nearly 17%, partially explained by the presence of extensive intraductal components, the possibility of poor aesthetic results, the surgeon's experience and the patients' desire[33].

Advanced disease characteristics were associated with SLNB in the adjusted model. Patients at stage III were 95% less likely to be submitted to SLNB compared with stage I, regardless of their NAC response, as demonstrated by the multiple regression model. Likewise, the worse response, the lower the odds of SLNB. Cases that did not present response to NAC had 55% lower odds of

SLNB compared to those with response, and those who underwent mastectomies were 90% less likely to undergo SLNB compared to conservative surgery. Similar results have been reported for other populations[17].

The observational design with retrospective data collection is a limitation of the study that may compromise its internal validity. Among possible biases, the effects of low magnitudes obtained in some association measures stand out. These associations, although statistically significant, may have been obtained at random, do not represent changes in clinical practice and should, therefore, be interpreted carefully.

In addition, a classification bias may have occurred as the data were acquired by an active medical record search; in addition, certain clinical variables as physical examination performed after NAC that could serve as adjustment variables were not obtained.

Immunohistochemistry of sentinel lymph nodes after NAC can also provide more accurate information on the existence of residual axillary disease. However, during the period when the patients were included in the study, this exam was not part of the institutional routine. The period between 2013 and 2015 was chosen because it was the beginning of the change in the institutional routine in relation to NAC and its new possibilities, expressed by the results of large studies carried out at that time.

Until 2012, this same institutional routine indicated systemic treatment before surgery only in patients considered inoperable, with radical surgery as a post-surgical indication, regardless of the treatment response. In other words, to indicate NAC for BC treatment was to "condemn" the patient to a mastectomy with axillary dissection, as well as to all its related consequences.

The strength of this study is the real-life evaluation, great number of women with homogeneous characteristics and presentation of safe results of SLNB performance after NAC, which may lead to decreased morbidity and lethality rates and improving the assistance to this population.

CONCLUSION

SLNB was performed after NAC in 29% of the cases investigated herein. After adjusting for possible confounding variables, patients in a more advanced clinical stage with a worse NAC response who underwent mastectomies were less likely to undergo SLNB.

CONTRIBUTIONS

Marcelo Adeodato Bello, Marcelo Morais Barbosa and Emanuelle Narciso Alvarez Valente contributed to the study design, acquisition, analysis and interpretation of the data and drafting of the manuscript. Anke Bergmann, Suzana Sales de Aguiar and Luiz Claudio Santos Thuler contributed to the study design, analysis and interpretation of the data and critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

The author Anke Bergmann declares a potential conflict of interests due to her being the scientific editor of INCA's Revista Brasileira de Cancerologia. The other authors do not have any conflict of interests.

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