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Axillary surgical approach in T1-T2N0M0 clinical breast cancer staging: Survival in a women's hospital cohort in Rio de Janeiro

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ABSTRACT

Introduction: The concerns regarding the prognosis and quality of life of patients with early breast cancer staging without lymph node involvement have increased, especially with regard to the axillary surgical approach. The aim of the present study was to determine overall survival and disease-free survival according to the axillary surgical approach. **Methods:** Retrospective cohort study of 827 women with clinical T1-T2N0M0 diagnosis attended at the Cancer Hospital III of the Brazilian National Cancer Institute, from January 2007 to December 2009, with a follow-up period of 60 months. Data were obtained from the Hospital Registry of Cancer through the medical records. **Results:** 683 women underwent sentinel lymph node biopsy and 144 underwent sentinel lymph node biopsy followed by axillary lymphadenectomy. After 5 years of follow-up, considering adjustment, it was observed overall survival (96.2% vs 93.6%; HR 0.98; 95%CI 0.42–2.29) and disease-free survival (93.7% vs 91.2%; HR 0.78; 95%CI 0.39–1.48) similar among patients undergoing either one or the other approach. In patients with micrometastasis, both overall (93.3%) and disease-free survival (100%) were higher in women who underwent only sentinel lymph node biopsy compared to those who underwent this procedure followed by axillary lymphadenectomy (OS: 87.5%; DFS: 90,7%), albeit not statistically significant. **Conclusions:** No difference was observed in overall or disease-free survival in patients with T1-T2N0M0 breast cancer staging according to axillary treatment (sentinel lymph node biopsy followed or not by axillary lymphadenectomy) in 60-month. In addition, no statistically significant differences in overall and disease-free survival were observed in women with sentinel node micrometastasis submitted to any of the approaches within 60 months.

KEYWORDS: breast cancer; sentinel lymph node biopsy; lymph node excision; survival analysis; disease-free survival.

INTRODUCTION

Breast cancer is the most common cancer and the leading cause of cancer-related deaths among women worldwide, with an incidence ranging from 36.1/100.000 women in countries with low human development index (HDI) to 75.6/100,000 women in very high HDI countries in 2020[1].

Surgery is the main treatment for breast cancer and can be complemented with radiotherapy, chemotherapy, hormone therapy, and biological therapy[2]. The surgical approach may be more conservative in the early stage of this neoplasm, depending on the presence or absence of axillary procedure. Thus, for proper axillary staging, surgical breast cancer treatment involves an approach through sentinel lymph node biopsy (SLNB) and/or axillary lymphadenectomy (AL). The AL intervention aims to establish lymph node status and to indicate the best treatment in order to improve survival and local disease control. However, it is often associated with increased early and late postoperative morbidity in breast cancer patients[3,4]. The first randomized studies to validate SLNB in breast cancer confirmed that this technique provides better disease control, improved survival, and accurate axillary staging, indicating that if the identified sentinel lymph node is not positive for cancer, the remaining lymph nodes display a high probability of being disease-free, so the patient is spared of AL and its complications[5,6].

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Thus, to minimize the complications generated by AL, in the 1990s, SLNB was incorporated to the diagnosis and therapeutic determination of breast cancer, marking a major advance in surgical treatment[7]. Currently, SLNB is the preferred staging method for breast cancer in clinically negative axilla patients with T1 or T2 classification[8]. Previously, due to the strongly negative prognostic value of axillary lymph node metastasis, AL used to be performed in patients with clinical lymph node metastasis, as well as in the case of positive SLNB. But, in recent years, this has changed, and a smaller number of AL has been performed for T1-T2 size neoplasms[9].

The evolution in sentinel lymph node evaluation methods has resulted in the frequent discovery of micrometastatic foci (≤2 mm in diameter) and isolated tumor cells, whose prognostic significance is still uncertain[7]. The literature shows a frequency of 4% to 8% of sentinel node micrometastasis[10,11], which could result in greater locoregional and distant recurrence, and possibly lower overall survival (OS) and disease-free survival (DFS) among patients undergoing SLNB compared to patients who underwent AL, as the presence of sentinel lymph node micrometastasis may indicate non-sentinel lymph node involvement[12]. However, several randomized studies have indicated that patients with negative SLNB fewer than three positive axillary lymph nodes or sentinel micrometastasis do not need to undergo AL[5,13-16]. It is known that most studies evaluating AL and lymph node micrometastasis in the survival of women with breast cancer have been conducted in developed countries, but the extrapolation of their results was not allowed for developing countries.

In Rio de Janeiro, the Cancer Hospital III of the Brazilian National Cancer Institute (HC-III/INCA) is reference for the treatment of breast cancer in this city and treats most breast cancer cases registered in the metropolitan region of the state, offering a rich database for exploring the survival of these patients. Taking this into consideration, this study aims to determine the OS and DFS of breast cancer patients with T1-T2N0M0 clinical classification, diagnosed and treated in the HC-III/INCA) from 2007–2009, according to the axillary surgical approach.

METHODS

An observational study was conducted with a cohort of 1,417 women presenting T1-T2N0M0 clinical stage breast cancer and treated at the HC-III/INCA, from 2007 to 2009, with a follow-up of 60 months. The original project was approved by the INCA Research Ethics Committees (under number 154/14) and by the National School of Public Health of the Oswaldo Cruz Foundation (under protocol 836,278).

The identification of T1N0M0 and T2N0M0 clinical staging was based on the Hospital Cancer Registry (HCR). The patients' physical and electronic medical records were obtained to extract sociodemographic, clinical and lifestyle-related (tobacco and alcohol consumption) data, as well as implemented treatments and outcome variables (disease status and vital status). The case condition and disease characteristics were validated by histopathological reports, which are analyzed at a single central INCA laboratory.

After reviewing medical records and histopathological reports, 590 out of the 1,417 patients were excluded (Figure 1), leaving a total study population of 827 women with tumors of up to 5 cm, negative axilla condition and no distant metastasis.

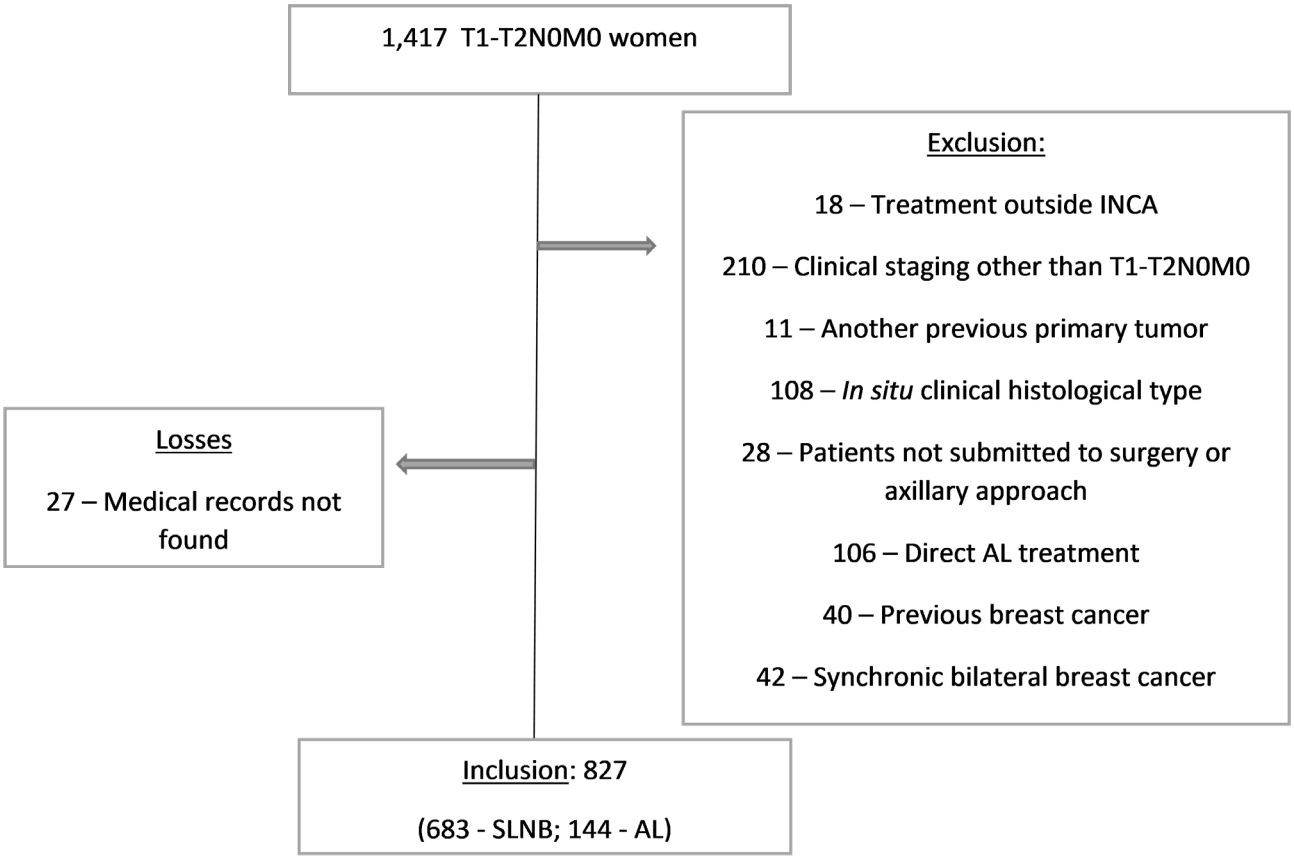
SLNB was defined as the removal of sentinel lymph nodes after identification, for histopathological examination[7]. AL was defined as the resection of at least one of the axillary levels. Lymph node metastases were classified according to the American Cancer Committee as metastases from 0.2 to 2.0 mm, while macrometastases were defined as those over 2.0 mm[17].

Regarding relapse, women with neoplastic cell proliferation in the operated region were considered as failures: skin, plastron, subcutaneous mesh, chest wall, lymphatic chains, and breast tissue in the case of conservative surgery; as well as those on which the disease spread to organs or tissues distant from the original tumor, confirmed by histopathological examination. Women who did not relapse were censored until the end of the study. Patients who were lost to follow-up were censored on the date of the last visit. DFS was characterized as the time elapsed between the date of surgery and the date of relapse diagnosis.

For the OS analysis, deaths from any cause occurring up to the end of 60 months were considered as a failure. Death information (date, cause, location) was obtained from physical medical records (death certificates) and electronic medical records. Women who were alive at the end of the study were censored, while those who were lost during follow-up were censored on the date of the last visit. OS was, then, characterized as the time elapsed between the date of breast cancer diagnosis and the date of death.

A descriptive analysis was performed using central tendency measures, as well as study cohort dispersion and frequency measures. Differences between means were assessed using Student's t-test for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Differences between proportions were evaluated using the Pearson's chi-square (χ^2) test for normally distributed variables and by the Fisher´s exact test for non-normally distributed variables. A significance level of 5% was considered for all assessments.

In addition, OS and DFS were estimated by the Kaplan-Meier analysis according to the axillary surgical approach. Differences between survival curves were assessed using the Log-rank test: 95%. The crude and adjusted relapse and death hazards ratios (HR), with their respective 95% confidence intervals (95%CI), were estimated using Cox proportional hazard regression analysis. Criteria for including variables in the final models were the statistical significance in the crude analyses (p-value≤0.20) and



SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; INCA: Brazilian National Cancer Institute.
Figure 1. Study sample selection flow.

biological importance; while for the model output, a significance level greater than 0.05 was considered. The fact that there were only 33 deaths limited the number of variables that could be used in a multivariate model without impacting model stability. Aiming to meet the criterion of a minimum number of failures in each axillary approach stratum for statistical modeling, a severity score was developed, consisting of six factors (0 to 6) for death outcome. This score included variables with statistically different distributions between the SLNB and SLNB+AL groups attributing weight to each variable category according to death risk, such as age (<40 years=0; 40–59 years=1; ≥60 years=2), clinical staging (T1N0M0=0; T2N0M0=1), histopathological grade (grade-1=0; grade-2=1; grade-3=2), and histopathological lymph node status (no metastasis=0; with metastasis=1). The total score was classified into three categories based on the mean, median and interquartile ranges. Thus, individuals who had a total severity score from 0 to 1 had characteristics that represented the lowest risk for death outcome, participants with scores from 2 to 4 had characteristics that conferred moderate risks of death, and those with scores from 5 to 6 had higher risks for death outcome.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) IBM software, version 20.0 for Windows.

RESULTS

The mean age of the women included in the study was 57 years old (±12.2). Most participants (65.7%) displayed clinical staging I (T1N0M0), 68.5% had tumors ≤2 cm, 40.1% presented histological grade 2, and 16.4% of the patients underwent removal of over 10 lymph nodes (Table 1). Regarding the axillary approach, 82.6% of women underwent just SLNB and 17.4% underwent SLNB+AL. Among the patients who underwent SLNB (n=683), most of them (61.9%) underwent conservative surgery, did not undergo chemotherapy (55.8%) but hormonal therapy (78%). Among those who underwent SLNB+AL (n=144), most underwent chemotherapy (80.6%), did mastectomy (57.6%), took hormonal therapy (86.8%), and presented distant recurrence (7.6%) (Table 1).

In patients who underwent SLNB alone, only two lymph nodes (±1.19) were removed on average, while those who underwent SLNB+AL removed an average of 17.8 lymph nodes (±5.35). No lymph node metastasis was observed in 699 (84.5%) patients, and 97.5% of these received only SLNB. In patients presenting lymph node metastasis (n=128), 2.5% underwent only SLNB, while 77.1% underwent SLNB+AL (Table 1). The median follow-up for both death and relapse in the cohort was of 60 months for both SLNB and SLNB+AL patients (Table 2). During this period, there were 33 deaths (SLNB: 24; SLNB+AL: 9) and 52 cases of relapse (SLNB: 40; SLNB+AL: 12).

Table 1. Distribution of sociodemographic and clinicopathologic status and treatment characteristics, according to axillary approach of the cohort of 827 women with breast cancer, treated at the Brazilian National Cancer Institute (2007–2009).

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Age				
<40	54 (6.5)	41 (6.0)	13 (9.0)	0.049
40–59	426 (51.5)	343 (50.2)	83 (57.6)	
≥60	347 (42.0)	299 (43.8)	48 (33.3)	
Skin color				
Non-White	267 (32.3)	229 (33.5)	38 (26.4)	0.096
White	560 (67.7)	454 (66.5)	106 (73.6)	
Marital status				
With a partner	431 (52.1)	346 (50.7)	85 (59.0)	0.068
No partner	396 (47.9)	337 (49.3)	59 (41.0)	
Schooling				
<8 years	350 (42.4)	296 (43.3)	54 (37.8)	0.220
≥8 years	476 (57.6)	387 (56.7)	89(62.2)	
Occupation				
Unemployed	32 (3.9)	28 (4.1)	4 (2.8)	0.482
External job	372 (45.3)	301 (44.5)	71 (49.3)	
At home	417 (50.8)	348 (51.4)	69 (47.9)	
Alcoholism				
No	597 (73.0)	487 (72.1)	110 (76.9)	0.243
Yes	221 (27.0)	188 (27.9)	33 (23.1)	
Smoking				
No	562 (68.2)	467 (68.6)	95 (66.4)	0.617
Yes	262 (31.8)	214 (31.4)	48 (33.6)	
BMI				
Low weight	35 (4.2)	30 (4.4)	5 (3.5)	0.583
Suitable weight	227 (27.4)	193 (28.3)	34 (23.6)	
Overweight	297 (35.9)	244 (35.7)	53 (36.8)	
Obesity	268 (32.4)	216 (31.6)	52 (36.1)	
Clinical staging				
T1N0M0 (I)	543 (65.7)	478 (70.0)	65 (45.1)	0.000
T2N0M0 (IIA)	284 (34.3)	205 (30.0)	79 (54.9)	
Tumor size				
T1	566 (68.5)	495 (72.6)	71 (49.3)	0.000
T2	253 (30.6)	184 (27.0)	69 (47.9)	
T3	7 (0.8)	3 (0.4)	4 (2.8)	
Histological type				
Lobular Invasive	52 (6.3)	40 (5.9)	12 (8.3)	0.249
Ductal Invasive	713 (86.2)	588 (86.1)	125 (86.8)	
Others	62 (7.5)	55 (8.1)	7 (4.9)	
Histological grade				
1	166 (22.7)	145 (24.2)	21 (16.0)	0.038
2	293 (40.1)	243 (40.6)	50 (38.2)	
3	271 (37.1)	211 (35.2)	60 (45.8)	
Number of lymph nodes removed				
1–3	619 (74.8)	619 (90.6)	0 (0.0)	0.000
4–10	72 (8.7)	64 (9.4)	8 (5.6)	
>10	136(16.4)	0 (0.0)	136 (94.4)	
Lymph node status				
No metastasis				
With metastasis				

Continue...

Table 1. Continuation.

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Sentinel lymph node metastasis				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
Micrometastasis	41 (5.0)	17 (2.5)	24 (16.7)	
Macrometastasis	87 (10.5)	0 (0.0)	87 (60.4)	
Status HER2[b]				
Negative	368 (74.8)	295 (75.4)	73 (72.3)	0.366
Positive	70 (14.2)	57 (14.6)	13 (12.9)	
Indeterminate	54 (11.0)	39 (10.0)	15 (14.9)	
Hormonal receptor				
Positive	694 (84.7)	564 (83.6)	130 (90.3)	0.042
Negative	125 (15.3)	111 (16.4)	14 (9.7)	
Triple negative[b]				
No	436 (90.8)	343 (89.8)	93 (94.9)	0.118
Yes	44 (9.2)	39 (10.2)	5 (5.1)	
Other primary cancer				
No	812 (98.2)	672 (98.4)	140 (97.2)	0.340
Yes	15 (1.8)	11 (1.6)	4 (2.8)	
Death				
No	794 (96.0)	659 (96.5)	135 (93.8)	0.127
Yes	33 (4.0)	24 (3.5)	9 (6.2)	
Lymph node status				
No metastasis	699 (84,5)	666 (97,5)	33 (22,9)	0,000
With metastasis	128(15,5)	17 (2,5)	111 (77,1)	
Locoregional recurrence				
No	808 (97.7)	665 (97.4)	143 (99.3)	0.158
Yes	19 (2.3)	18 (2.6)	1 (0.7)	
Distance recurrence				
No	790 (95.5)	657 (96.2)	133 (92.4)	0.043
Yes	37 (4.5)	26 (3.8)	11 (7.6)	
Breast surgery				
Conservative	484 (58.5)	423 (61.9)	61 (42.4)	0.000
Mastectomy	343 (41.5)	260 (38.1)	83 (57.6)	
Breast reconstruction				
No	681 (82.3)	557 (81.6)	124 (86.1)	0.192
Yes	146 (17.7)	126 (18.4)	20 (13.9)	
Chemotherapy				
No	409 (49.5)	381 (55.8)	28 (19.4)	0.000
Yes	418 (50.5)	302 (44.2)	116 (80.6)	
Radiotherapy				
No	328 (39.7)	265 (38.8)	63 (43.8)	0.270
Yes	499 (60.3)	418 (61.2)	81 (56.2)	
Hormonal therapy				
No	169 (20.4)	150 (22.0)	19 (13.2)	0.018
Yes	658 (79.6)	533 (78.0)	125 (86.8)	
Target therapy				
No	790 (95.5)	655 (95.9)	135 (93.8)	0.257
Yes	37 (4.5)	28 (4.1)	9 (6.2)	
Severity score[c]				
0–1	78 (9.4)	78 (11.4)	0 (0.0)	0.000
2–4	675 (81.6)	573 (83.9)	102 (70.8)	
5–6	74 (8.9)	32 (4.7)	42 (29.2)	

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index; HER2: human epidermal growth factor receptor 2; χ^2: Pearson's χ^2 test; Non-white: black, brown. *The total value may change due to missing values. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy. [b]The analysis of molecular markers has become routine at Brazilian National Cancer Institute starting 2011, not all patients underwent the tests. [c]Severity score includes age, clinical staging, histological grade, and lymph node status.

Table 2. Follow-up time (death and recurrence), according to the axillary approach, of the cohort of 827 women with breast cancer treated at the Brazilian National Cancer Institute (2007–2009).

	Total	Axillary surgery	
		SLNB	SLNB+AL[a]
Follow-up time until death			
Mean (SD) n (%)	56.66 (9.93)	56.77 (9.61)	56.18 (11.33)
Median (months)	60.00	60.00	60.00
Minimum–Maximum (months)	1.7–60.0	1.7–60.0	6.8–60.0
Follow-up time until recurrence			
Mean (SD) n (%)	54.86 (12.17)	54.98 (11.82)	54.29 (13.72)
Median (months)	60.00	60.00	60.00
Minimum-Maximum (months)	0.8–60.0	0.8–60.0	2.1–60.0

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; SD: standard deviation. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy.

Among patients presenting only sentinel lymph node micrometastasis, it was observed higher survival rate in those undergoing SLNB alone (OS: 93.3%; DFS: 100%) compared to those who underwent SLNB+AL (OS=87.5%; DFS=90.7%), albeit without any statistical significance. All patients with sentinel node macrometastasis underwent AL after SLNB, hindering comparisons (Table 3).

The risk of relapse in women undergoing SLNB was not statistically different from those undergoing SLNB+AL (Figure 2). Disease-free 5-year survival did not differ significantly between the two approaches (SLNB: 93.7%; SLNB+AL: 91.2%; Log-Rank p=0.264). Thus, estimated risk of crude relapse (HR 0.69; 95%CI 0.36–1.32) and adjusted relapse (HR 0.78; 95%CI 0.39–1.48) comparing SLNB with SLNB+AL were not statistically significant, even when adjusted for age, clinical staging, grade, and hormone therapy (Figure 2).

Overall 5-year survival was 96.2% in SLNB and 93.6% in SLNB+AL patients (Log-Rank p=0.131) (Table 3). The crude HR of death between SLNB and SLNB+AL group was of 0.56 (95%CI 0.26–1.20; p=0.136). The severity score-adjusted death risk analysis, which included age, clinical staging, histopathological grade, and histopathological lymph node status, for the SLNB group compared to the SLNB+AL group was 0.98 (95%CI 0.42–2.29) (Figure 3).

DISCUSSION

Changes in breast cancer presentation and treatment, as well as the selection of systemic treatment based on tumor biology, have raised questions about the need for AL in some patients presenting sentinel node metastasis. Currently, the biology of breast cancer is much better understood than it was when AL was introduced. It has since been recognized that breast cancer biology, rather than the extent of surgery, is a major determinant of both systemic and locoregional metastasis risk, paving the way for new surgical approaches such as SLNB[18].

This study evaluated 827 women with clinical stage T1-T2N0M0 breast cancer who underwent SLNB and SLNB+AL, and no statistically significant differences were found after 60 months in the OS or DFS of women who underwent SLNB when compared to those who underwent SLNB+AL. Similar results were reported by Canavese et al.[19] in a randomized clinical trial conducted at the National Cancer Research Institute of Italy (Genoa, Italy), where the non-inferiority of SLNB relative to AL was noted for 2,570 patients with early breast cancer staging (<3 cm). The authors observed that the 5-year OS for both groups was of 97.2% (Log-Rank p=0.697). DFS was also not statistically different between SLNB and AL groups (AL: 89.8%; SLNB: 94.5%; Log-Rank p=0.715).

The benefits of SLNB on survival and postoperative complications in early stage breast cancer patients (T1-T2N0M0), including accuracy in predicting axillary status, have been demonstrated in several studies over time[14,15,19-22]. Based on the results, a negative SLNB outcome in these patients is considered sufficient to rule out the possibility of metastasis in other axillary lymph nodes and to prevent future AL, reducing short-term morbidity and improving quality of life[4,23,24]. However, information on the long-term effects of SLNB compared to routine AL is still considered limited.

On the other hand, an indication of AL has always been considered safe, as it removes all axilla disease, promoting greater locoregional control and providing important information for systemic and prognostic therapy. Nonetheless, this approach is associated with complications such as pain, reduced motion range, paresthesia, axillary web syndrome, winged scapula, and lymphedema[25,26]. Thus, SLNB has been rapidly integrated, as it avoids AL in a large number of patients with early breast cancer staging, while also providing important information to guide adjuvant treatment.

Randomized controlled trials have compared OS and DFS among patients who underwent SLNB or SLNB+AL approach in the presence of negative sentinel lymph nodes. The results of these studies showed no negative effect on OS and DFS for the

Table 3. Overall survival and crude hazard ratio according to sociodemographic, clinicopathologic and treatment characteristics in the cohort of 827 women with breast cancer treated at the Brazilian National Cancer Institute (2007–2009).

Overall (n=827)	Death n (%)	Overall Survival (%)			Crude HR (95%CI)
		SLNB	SLNB+AL[a]	LR p-value	
	33	96.2	93.6	0.131	
Age					
<40	2 (6.1)	97.4	92.3	0.396	1 (Ref.)
40–59	18 (54.5)	95.4	96.3	0.765	1.11 (0.26–4.77)
≥60	13 (39.4)	97.0	89.4	0.008	1.04 (0.23–4.62)
Skin color					
Non-White	12 (36.4)	95.3	94.4	0.721	1 (Ref.)
White	21 (63.6)	96.7	93.4	0.101	0.83 (0.41–1.69)
Marital status					
with a partner	18 (54.5)	95.7	95.2	0.783	1 (Ref.)
No partner	15 (45.5)	96.7	91.4	0.045	0.92 (0.46–1.82)
Schooling					
<8 years	16 (48.5)	95.6	92.4	0.264	1 (Ref.)
≥8 years	17 (51.5)	96.7	94.3	0.262	0.77 (0.39–1.52)
Occupation					
Unemployed	3 (9.5)	87.1	100.0	0.463	1 (Ref.)
External job	13 (39.4)	96.5	95.7	0.715	0.36 (0.10–1.27)
At home	17 (51.5)	96.6	91.2	0.032	0.44 (0.13–1.49)
Alcoholism					
No	19 (57.6)	97.2	94.5	0.137	1 (Ref.)
Yes	14 (42.4)	93.6	90.6	0.436	2.00 (1.00–3.99)
Smoking					
No	24 (72.7)	96.1	92.5	0.103	1 (Ref.)
Yes	9 (27.3)	96.4	95.7	0.761	0.80 (0.37–1.71)
BMI					
Low weight+Suitable weight	8 (24.2)	97.0	94.6	0.413	1 (Ref.)
Overweight+Obesity	25 (75.8)	95.8	93.3	0.220	1.41 (0.63–3.12)
Clinical staging					
T1N0M0 (I)	11 (33.3)	97.5	100.0	0.212	1 (Ref.)
T2N0M0 (IIA)	22 (66.7)	93.2	88.4	0.144	3.89 (1.89–8.03)
Tumor size					
T1 (≤2 cm)	14 (42.4)	97.2	98.6	0.518	1 (Ref.)
T2-T3 (>2–7,5cm)	19 (57.6)	93.5	88.7	0.139	3.00 (1.51–6.00)
Lymph node status					
No metastasis	26 (78.8)	96.3	90.5	0.073	1 (Ref.)
With metastasis	8 (21.2)	93.3	94.5	0.932	1.45 (0.63–3.33)
Sentinel lymph node metastasis					
No metastasis	26 (78.8)	96.3	90.5	0.073	1 (Ref.)
Micrometastasis	4 (12.1)	93.3	87.5	0.485	2.66 (0.93–7.63)
Macrometastasis	3 (9.1)	–	96.5	–	0.90 (0.27–2.97)
Number lymph nodes removed					
1–3	23 (69.7)	96.0	–	–	1 (Ref.)
4–10	2 (6.1)	98.4	87.5	0.075	0.75 (0.18-3.20)
>10	8 (24.2)	–	94.0	–	1.59 (0.71-3.56)
Histological grade					
1	1 (3.1)	100	95.2	0.011	1 (Ref.)
2–3	31 (96.9)	94.6	92.6	0.338	9.12 (1.24–66.81)

Continue...

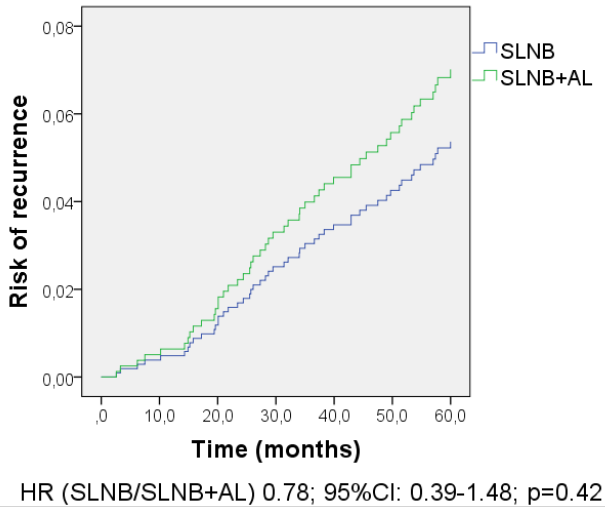
Table 3. Continuation.

Overall (n=827)	Death n (%)	Overall Survival (%)			Crude HR (95%CI)
		SLNB	SLNB+AL[a]	LR p-value	
	33	96.2	93.6	0.131	
Status HER2[b]					
Negative	14 (70.0)	96.8	93.0	0.117	1 (Ref.)
Positive	1 (5.0)	98.1	100	0.617	0.36 (0.05–2.76)
Indeterminate	5 (25.0)	85.4	100.0	0.138	2.61 (0.94–7.24)
Triple negative[b]					
No	18 (94.7)	96.0	94.6	0.497	1 (Ref.)
Yes	1 (5.3)	96.7	100.0	0.796	0.60 (0.08–4.51)
Hormonal receptor					
Positive	27 (81.8)	96.2	94.5	0.346	1 (Ref.)
Negative	6 (18.2)	96.0	84.6	0.049	1.28 (0.53–3.09)
Breast surgery					
Conservative	15 (45.5)	96.4	98.3	0.460	1 (Ref.)
Mastectomy	18 (54.5)	95.9	90.1	0.035	1.69 (0.85–3.36)
Histological type					
Lobular Invasive	1 (3,0)	97,4	100,0	0,591	1
Ductal Invasive	31 (93,9)	96,0	92,6	0,084	2,33 (0,32-17,10)
Others	1 (3,0)	98,0	100,0	0,708	0,89 (0,05-14,16)
Hormonal therapy					
No	10 (30.3)	96.2	72.7	0.000	1 (Ref.)
Yes	23 (69.7)	96.2	96.7	0.825	0.53 (0.25–1.11)
Chemotherapy					
No	13 (39.4)	96.8	92.9	0.225	1 (Ref.)
Yes	20 (60.6)	95.5	93.8	0.427	1.44 (0.72–2.89)
Radiotherapy					
No	16 (48.5)	96.4	88.8	0.011	1 (Ref.)
Yes	17 (51.5)	96.1	97.4	0.603	0.69 (0.35–1.36)
Target therapy					
No	33 (100)	96.0	93.2	0.114	1 (Ref.)
Yes	0 (0.0)	100.0	100.0	–	0.05 (0.00–54.54)
Other primary					
No	29 (87.9)	96.6	94.2	0.139	1 (Ref.)
Yes	4 (12.1)	72.7	75.0	0.964	8.16 (2.87–23.21)
Recurrence					
No	11 (33.3)	98.7	97.7	0.371	1 (Ref.)
Yes	22 (66.7)	55.2	50.0	0.445	37.43(18.10-77.40)
Severity score[c]					
0–1	1 (3.0)	98.7	-	-	1 (Ref.)
2–4	22 (66.7)	96.2	98.0	0.395	2. 60 (0.35–19.26)
5–6	10 (30.3)	90.0	82.9	0.329	11.79 (1.51–92.15)

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index; Non-white: black, brown; LR: log-rank; HR: hazard ratio; 95%CI: confidence interval 95%. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy; [b]The analysis of molecular markers has become routine at Brazilian National Cancer Institute starting 2011, not all patients underwent the tests; [c]Severity score includes age, clinical staging, histological grade and lymph node status.

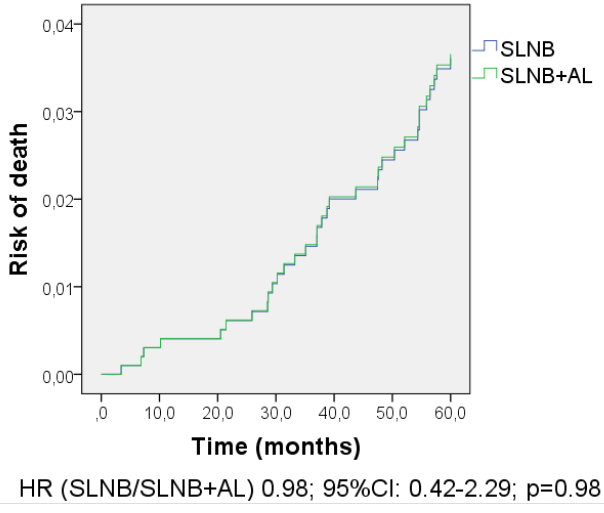
SLNB technique when compared to AL[6,19,26-28]. Two meta-analyses, which included all major randomized controlled trials evaluating the efficacy of SLNB in metastasis-free axilla (pN0), further reinforced the favorable effect of SLNB on survival and postoperative morbidity[29,30]. Thus, the results of this study corroborate previous studies, as it was observed no significant difference in overall and disease-free survival among patients who did not present lymph node metastasis (SLNB: 96.3; SLNB+AL: 90,7; p=0.073).

Although one of the inclusion criteria in this study was initial breast cancer staging (T1-T2N0M0) after the axillary approach, patients with lymph node involvement (micrometastasis: 41; macrometastasis: 87) were detected in the final histopathological examination. Of the women who presented micrometastasis, 17 underwent SLNB and 24 underwent SLNB+AL. On the other hand, all patients with macrometastasis received AL after SLNB. The OS among the 41 patients presenting micrometastasis was higher in those who underwent SLNB (93.3%) compared to those who underwent SLNB+AL (87.5%), but with no statistical significance (Log-Rank p=0.485). Similarly, no statistically significant differences in DFS were observed between both approaches (SLNB: 100%; SLNB+AL: 90.7%; Log-Rank p=0.241). These results corroborate previous studies, which reported that AL can be safely avoided in women with early breast cancer with sentinel lymph node micrometastasis[14,15,31]. The results of our study are worth considering (even though it is an observational research) since the multicenter clinical trials that compared the two types of approach in patients with micrometastasis did not include Brazilian or Latin American treatment centers.



SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; HR: hazard ratio; 95%CI: confidence interval 95%.

Figure 2. Adjusted hazard ratio model for recurrence according to axillary surgery approach (adjusted by age, clinical stage, grade, and hormonal therapy).



SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; HR: hazard ratio; 95%CI: confidence interval 95%.

Figure 3. Adjusted hazard ratio model for death according to axillary surgery approach (adjusted by severity score–age, clinical stage, grade, and lymph node status).

Several studies have shown that approximately 34.3% to 85.7% of patients with sentinel lymph node metastasis will not present additional nodal disease[32]. In the presence of micrometastasis or isolated tumor cells, the risk of additional lymph node involvement is even lower, of 20% and 12%, respectively[33,34]. Due to these findings, the performance of AL, even in the presence of positive sentinel nodes, becomes questionable, since most of them will not have additional nodal load.

According to the results obtained in this study, it was observed no significant difference among women undergoing SLNB and SLNB+AL concerning the frequency of locoregional recurrence. A low survival rate was observed in the OS analysis of patients who presented some type of relapse, but there was no significant difference between both axillary approaches (SLNB: 55.2%; SLNB+AL 50%; Log-rank p=0.445). Two large retrospective studies[35,36] observed no negative impact on OS and on axillary recurrence, even without AL, in the presence of positive sentinel lymph nodes.

The absence of significant differences between OS and DFS among the approaches observed in this study was confirmed by the analysis of gross and adjusted risks of death (crude HR 0.56; 95%CI 0.26–1.20; adjusted HR 0.98; 95%CI 0.42–2.29) and for relapse (crude HR 0.69; 95%CI 0.36–1.32; adjusted HR 0.78; 95%CI 0.39–1.48), indicating a lower risk for SLNB, but without statistical significance. These results corroborate the findings of two main randomized controlled trials that also compared the performance of SLNB and AL in patients with early staging and limited axillary disease. The American College of Surgeons Oncology Group (ACOSOG) Z0011 study concerning T1 and T2 patients who underwent conservative surgery, with one or two positive lymph nodes, observed an overall 5-year survival of 91.8% in the AL group and 92.5% in SLNB patients. Similarly, disease-free 5-year survival was of 82.2% in the AL group and 83.9% in those who underwent only SLNB. Regional recurrence was also

similar in both groups (AL: 0.5%; SLNB: 0.9%). The risk of death was similar for both approaches, even after age and adjuvant therapy adjustment (HR=0.87; 95%CI 0.62–1.23).) Also, the risk of recurrence was not statistically different between the axillary approaches, even after adjustment for age and adjuvant treatment (HR 0.88; 95%CI 0.62–1.25)[14]. Another clinical trial conducted by the International Breast Cancer Study Group (IBCSG), after an average follow-up of 5 years, also observed that AL could be safely omitted in patients with lymph node micrometastasis, with no inferiority compared to the SLNB technique[15].

Since the confirmation of non-inferiority of SLNB over AL, the conservative approach has been incorporated into the daily practice of cancer treatment centers, as breast surgeons' experience and confidence in the SLNB approach has increased[37-39]. A Dutch study assessing surgeon practice standards regarding SLNB and AL from January 1993 to July 2014 found that the number of patients undergoing SLNB without AL increased from 0% in 1993-1994 to 69% in 2013-2014. In the same period, the number of patients undergoing AL decreased from 88.8% to 18.7%[40].

One of the limitations of the present study includes such as those inherent to retrospective studies. Data collection based on medical records may introduce limitations concerning the quality of the data obtained from routine appointments. Another limitation is related to the small number of patients with micrometastasis in this sample, which does not allow for adjusted analyses concerning the effect of SLNB on death and relapse risks. Thus, further studies with a larger number of patients presenting micrometastasis are required. Finally, another limitation is the small number of death outcomes in the 5-year follow-up period, which limits the analysis of the independent effect of each of the variables such as age, clinical stage, histopathological degree and lymph node involvement. However, this limitation was addressed through the creation of the "severity score" variable, which was a combination of the effect of these variables. This strategy allowed the combined effect of these variables to be evaluated, without promoting overfitting of the model.

Nevertheless, this study comprises a high number of patients with T1-T2N0M0 staging, with a complete 60-month follow-up of almost 90% of the cohort, in favor of the consistency of our findings, so that estimates would not be distorted by selection biases. In addition, as these data are from the same institution, all procedures followed a standardized protocol and were less subject to professional conduct variations. Another important point of this study is that it presents the results of developing countries. As most of the studies that evaluated AL and lymph node micrometastases in the survival of women with breast cancer have been conducted in developed countries and they do not allow for results extrapolation to developing countries, this further reinforces the importance of this study.

Findings reported herein indicate that the axillary approach using the SLNB method is equivalent to AL for OS and DFS after five years, regardless of the adjustment variables.

In addition, no statistically significant differences in OS and DFS were observed after 60 months in women with axillary lymph node micrometastasis undergoing SLNB compared to those undergoing SLNB+AL. Due to the small number of micrometastasis cases observed in this study, further research, with larger sample sizes, are required to evaluate the non-inferiority of SLNB compared to AL in the overall DFS of patients with T1-T2N0M0 breast cancer.

AUTHORS' CONTRIBUTIONS

FOM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AB: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. RJK: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. DMT: Validation, Visualization, Writing – original draft, Writing – review & editing. EANF: Conceptualization, Investigation, Methodology, Writing – review & editing. RMC: Conceptualization, Investigation, Methodology, Writing – review & editing. FOF: Conceptualization, Investigation, Methodology, Writing – review & editing. IFS: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing

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ERRATUM

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In the manuscript "Axillary surgical approach in T1-T2N0M0 clinical breast cancer staging: Survival in a women's hospital cohort in Rio de Janeiro", DOI: 10.29289/2594539420220036, published in the Mastology 2022;32:e20220036, on pages 4-5:

Where it reads:

Table 1. Distribution of sociodemographic and clinicopathologic status and treatment characteristics, according to axillary approach of the cohort of 827 women with breast cancer, treated at the Brazilian National Cancer Institute (2007–2009).

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Age				
<40	54 (6.5)	41 (6.0)	13 (9.0)	0.049
40–59	426 (51.5)	343 (50.2)	83 (57.6)	
≥60	347 (42.0)	299 (43.8)	48 (33.3)	
Skin color				
Non-White	267 (32.3)	229 (33.5)	38 (26.4)	0.096
White	560 (67.7)	454 (66.5)	106 (73.6)	
Marital status				
With a partner	431 (52.1)	346 (50.7)	85 (59.0)	0.068
No partner	396 (47.9)	337 (49.3)	59 (41.0)	
Schooling				
<8 years	350 (42.4)	296 (43.3)	54 (37.8)	0.220
≥8 years	476 (57.6)	387 (56.7)	89(62.2)	
Occupation				
Unemployed	32 (3.9)	28 (4.1)	4 (2.8)	0.482
External job	372 (45.3)	301 (44.5)	71 (49.3)	
At home	417 (50.8)	348 (51.4)	69 (47.9)	
Alcoholism				
No	597 (73.0)	487 (72.1)	110 (76.9)	0.243
Yes	221 (27.0)	188 (27.9)	33 (23.1)	
Smoking				
No	562 (68.2)	467 (68.6)	95 (66.4)	0.617
Yes	262 (31.8)	214 (31.4)	48 (33.6)	
BMI				
Low weight	35 (4.2)	30 (4.4)	5 (3.5)	0.583
Suitable weight	227 (27.4)	193 (28.3)	34 (23.6)	
Overweight	297 (35.9)	244 (35.7)	53 (36.8)	
Obesity	268 (32.4)	216 (31.6)	52 (36.1)	
Clinical staging				
T1N0M0 (I)	543 (65.7)	478 (70.0)	65 (45.1)	0.000
T2N0M0 (IIA)	284 (34.3)	205 (30.0)	79 (54.9)	
Tumor size				
T1	566 (68.5)	495 (72.6)	71 (49.3)	0.000
T2	253 (30.6)	184 (27.0)	69 (47.9)	
T3	7 (0.8)	3 (0.4)	4 (2.8)	
Histological type				
Lobular Invasive	52 (6.3)	40 (5.9)	12 (8.3)	0.249
Ductal Invasive	713 (86.2)	588 (86.1)	125 (86.8)	
Others	62 (7.5)	55 (8.1)	7 (4.9)	
Histological grade				
1	166 (22.7)	145 (24.2)	21 (16.0)	0.038
2	293 (40.1)	243 (40.6)	50 (38.2)	
3	271 (37.1)	211 (35.2)	60 (45.8)	
Number of lymph nodes removed				
1–3	619 (74.8)	619 (90.6)	0 (0.0)	0.000
4–10	72 (8.7)	64 (9.4)	8 (5.6)	
>10	136(16.4)	0 (0.0)	136 (94.4)	
Lymph node status				
No metastasis				
With metastasis				

Continue...

Table 1. Continuation.

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Sentinel lymph node metastasis				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
Micrometastasis	41 (5.0)	17 (2.5)	24 (16.7)	
Macrometastasis	87 (10.5)	0 (0.0)	87 (60.4)	
Status HER2[b]				
Negative	368 (74.8)	295 (75.4)	73 (72.3)	0.366
Positive	70 (14.2)	57 (14.6)	13 (12.9)	
Indeterminate	54 (11.0)	39 (10.0)	15 (14.9)	
Hormonal receptor				
Positive	694 (84.7)	564 (83.6)	130 (90.3)	0.042
Negative	125 (15.3)	111 (16.4)	14 (9.7)	
Triple negative[b]				
No	436 (90.8)	343 (89.8)	93 (94.9)	0.118
Yes	44 (9.2)	39 (10.2)	5 (5.1)	
Other primary cancer				
No	812 (98.2)	672 (98.4)	140 (97.2)	0.340
Yes	15 (1.8)	11 (1.6)	4 (2.8)	
Death				
No	794 (96.0)	659 (96.5)	135 (93.8)	0.127
Yes	33 (4.0)	24 (3.5)	9 (6.2)	
Lymph node status				
No metastasis	699 (84,5)	666 (97,5)	33 (22,9)	0,000
With metastasis	128(15,5)	17 (2,5)	111 (77,1)	
Locoregional recurrence				
No	808 (97.7)	665 (97.4)	143 (99.3)	0.158
Yes	19 (2.3)	18 (2.6)	1 (0.7)	
Distance recurrence				
No	790 (95.5)	657 (96.2)	133 (92.4)	0.043
Yes	37 (4.5)	26 (3.8)	11 (7.6)	
Breast surgery				
Conservative	484 (58.5)	423 (61.9)	61 (42.4)	0.000
Mastectomy	343 (41.5)	260 (38.1)	83 (57.6)	
Breast reconstruction				
No	681 (82.3)	557 (81.6)	124 (86.1)	0.192
Yes	146 (17.7)	126 (18.4)	20 (13.9)	
Chemotherapy				
No	409 (49.5)	381 (55.8)	28 (19.4)	0.000
Yes	418 (50.5)	302 (44.2)	116 (80.6)	
Radiotherapy				
No	328 (39.7)	265 (38.8)	63 (43.8)	0.270
Yes	499 (60.3)	418 (61.2)	81 (56.2)	
Hormonal therapy				
No	169 (20.4)	150 (22.0)	19 (13.2)	0.018
Yes	658 (79.6)	533 (78.0)	125 (86.8)	
Target therapy				
No	790 (95.5)	655 (95.9)	135 (93.8)	0.257
Yes	37 (4.5)	28 (4.1)	9 (6.2)	
Severity score[c]				
0–1	78 (9.4)	78 (11.4)	0 (0.0)	0.000
2–4	675 (81.6)	573 (83.9)	102 (70.8)	
5–6	74 (8.9)	32 (4.7)	42 (29.2)	

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index; HER2: human epidermal growth factor receptor 2; χ^2: Pearson's χ^2 test; Non-white: black, brown. *The total value may change due to missing values. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy. [b]The analysis of molecular markers has become routine at Brazilian National Cancer Institute starting 2011, not all patients underwent the tests. [c]Severity score includes age, clinical staging, histological grade, and lymph node status.

It should read:

Table 1. Distribution of sociodemographic and clinicopathologic status and treatment characteristics, according to axillary approach of the cohort of 827 women with breast cancer, treated at the Brazilian National Cancer Institute (2007–2009).

	Total*	Axillary surgery N(%)		x^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Age				
<40	54 (6.5)	41 (6.0)	13 (9.0)	0.049
40–59	426 (51.5)	343 (50.2)	83 (57.6)	
≥60	347 (42.0)	299 (43.8)	48 (33.3)	
Skin color				
Non-White	267 (32.3)	229 (33.5)	38 (26.4)	0.096
White	560 (67.7)	454 (66.5)	106 (73.6)	
Marital status				
With a partner	431 (52.1)	346 (50.7)	85 (59.0)	0.068
No partner	396 (47.9)	337 (49.3)	59 (41.0)	
Schooling				
<8 years	350 (42.4)	296 (43.3)	54 (37.8)	0.220
≥8 years	476 (57.6)	387 (56.7)	89(62.2)	
Occupation				
Unemployed	32 (3.9)	28 (4.1)	4 (2.8)	0.482
External job	372 (45.3)	301 (44.5)	71 (49.3)	
At home	417 (50.8)	348 (51.4)	69 (47.9)	
Alcoholism				
No	597 (73.0)	487 (72.1)	110 (76.9)	0.243
Yes	221 (27.0)	188 (27.9)	33 (23.1)	
Smoking				
No	562 (68.2)	467 (68.6)	95 (66.4)	0.617
Yes	262 (31.8)	214 (31.4)	48 (33.6)	
BMI				
Low weight	35 (4.2)	30 (4.4)	5 (3.5)	0.583
Suitable weight	227 (27.4)	193 (28.3)	34 (23.6)	
Overweight	297 (35.9)	244 (35.7)	53 (36.8)	
Obesity	268 (32.4)	216 (31.6)	52 (36.1)	
Clinical staging				
T1N0M0 (I)	543 (65.7)	478 (70.0)	65 (45.1)	0.000
T2N0M0 (IIA)	284 (34.3)	205 (30.0)	79 (54.9)	
Tumor size				
T1	566 (68.5)	495 (72.6)	71 (49.3)	0.000
T2	253 (30.6)	184 (27.0)	69 (47.9)	
T3	7 (0.8)	3 (0.4)	4 (2.8)	
Histological type				
Lobular Invasive	52 (6.3)	40 (5.9)	12 (8.3)	0.249
Ductal Invasive	713 (86.2)	588 (86.1)	125 (86.8)	
Others	62 (7.5)	55 (8.1)	7 (4.9)	
Histological grade				
1	166 (22.7)	145 (24.2)	21 (16.0)	0.038
2	293 (40.1)	243 (40.6)	50 (38.2)	
3	271 (37.1)	211 (35.2)	60 (45.8)	
Number of lymph nodes removed				
1–3	619 (74.8)	619 (90.6)	0 (0.0)	0.000
4–10	72 (8.7)	64 (9.4)	8 (5.6)	
>10	136(16.4)	0 (0.0)	136 (94.4)	
Sentinel lymph node metastasis				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
Micrometastasis	41 (5.0)	17 (2.5)	24 (16.7)	
Macrometastasis	87 (10.5)	0 (0.0)	87 (60.4)	

Continue...

Table 1. Continuation.

	Total*	Axillary surgery N(%)		x^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Status HER2[b]				
Negative	368 (74.8)	295 (75.4)	73 (72.3)	0.366
Positive	70 (14.2)	57 (14.6)	13 (12.9)	
Indeterminate	54 (11.0)	39 (10.0)	15 (14.9)	
Hormonal receptor				
Positive	694 (84.7)	564 (83.6)	130 (90.3)	0.042
Negative	125 (15.3)	111 (16.4)	14 (9.7)	
Triple negative[b]				
No	436 (90.8)	343 (89.8)	93 (94.9)	0.118
Yes	44 (9.2)	39 (10.2)	5 (5.1)	
Other primary cancer				
No	812 (98.2)	672 (98.4)	140 (97.2)	0.340
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Lymph node statu				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
With metastasis	128(15.5)	17 (2.5)	111 (77.1)	
Locoregional recurrence				
No	808 (97.7)	665 (97.4)	143 (99.3)	0.158
Yes	19 (2.3)	18 (2.6)	1 (0.7)	
Distance recurrence				
No	790 (95.5)	657 (96.2)	133 (92.4)	0.043
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Severity score[c]				
0–1	78 (9.4)	78 (11.4)	0 (0.0)	0.000
2–4	675 (81.6)	573 (83.9)	102 (70.8)	
5–6	74 (8.9)	32 (4.7)	42 (29.2)	

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index; HER2: human epidermal growth factor receptor 2; x^2: Pearson's x^2 test; Non-white: black, brown. *The total value may change due to missing values. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy. [b]The analysis of molecular markers has become routine at Brazilian National Cancer Institute starting 2011, not all patients underwent the tests. [c]Severity score includes age, clinical staging, histological grade, and lymph node status.

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