# Sentinel Node Biopsy After Neoadjuvant Chemotherapy In Breast Cancer: Real Life Results

**Marcelo Adeodato Bello** ( marcelobello2@gmail.com )
Instituto Nacional do Cancer: Instituto Nacional de Cancer https://orcid.org/0000-0002-0843-6066
**Anke Bergmann**
Instituto Nacional de Cancer
**Suzana Sales Aguiar**
Instituto Nacional de Cancer
**Marcelo Morais Barbosa**
Instituto Nacional de Cancer
**Emanuelle Narciso Alvarez Valente**
Instituto Nacional de Cancer
**Luiz Claudio Santos Thuler**
Instituto Nacional de Cancer

**Research Article**

**Keywords:** Chemotherapy, Breast Neoplasms, Lymph Node Excision, Sentinel Lymph Node Biopsy.

**Posted Date:** June 1st, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-563561/v1

# Abstract

**Purpose:** compare demographic, clinical and treatment characteristics of women undergoing neoadjuvant chemotherapy (NAC) for breast cancer (BC) treatment according to the axillary approach and analyze factors associated with the indication of sentinel lymph node biopsy (SLNB) in a real-life scenario.

**Methods:** retrospective cohort study in women diagnosed with BC with indication for NAC. Demographic, clinical, tumor, surgical and adjuvant treatment variables were obtained.. A univariate logistic regression was performed to evaluate the independent factors associated with SLNB indication and a multiple model was applied for adjustments.

**Results:** A total of 918 patients were included in this study, 161 (17.5%) of whom underwent SLNB, 105 (11.4%) who underwent SLNB followed by AL and 652 (71.0%) who underwent AL only. Concerning the adjusted model, women in stage III were 95% less likely to be submitted to an SLNB (OR = 0.05 95% CI 0.01-0.17; p<0.001) compared to those in stage I. Women who underwent mastectomies exhibited a 90% lower chance of undergoing SLNB than those who underwent conservative surgery (95% CI 0.06-0.17; p <0.001). Considering NAC responses, cases with no response or presenting disease progression exhibited a 55% lower chance of undergoing SLNB compared to those displaying a total response (OR = 0.45 95% CI 0.24-0.82; p = 0.009).

**Conclusion:** SLNB was performed in 29% of the patients following NAC. Patients presenting a more advanced clinical stage of the disease with a worse NAC response and those who underwent mastectomies were less likely to undergo SLNB.


# Introduction

Breast cancer (BC) is the most common cancer among women. Its incidence corresponds to 11.6% of all malignancies (about 2.1 million new cases worldwide in 2018) and to 24.2% 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, representing 29.7% of new cancer cases in women per year. A total of 66,280 new cases are estimated for each year of the 2020-2022 triennium, corresponding to an estimated risk of 61.61 new cases per 100,000 women [2].

Throughout history, BC treatment has undergone numerous transformations, as 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 applied in 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, such as conducting clinical studies on the effectiveness of antineoplastic *in vivo* agents, evaluating predictive and prognostic biomarkers in tumor responses and performing conservative surgical treatments with better aesthetic results, not only in cases of advanced carcinoma but also in early breast carcinomas. Another more recently observed neoajuvancy benefit comprises the possibility of adding new drugs to the adjuvant if no pathological response is observed during the first systemic approach [3-8].

Regarding axillary approaches after NAC, classic surgery consists in axillary lymphadenectomy (AL), and studies seeking 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 [7,9-12].

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.

# Methods

A cohort study with retrospective data collection was conducted in women diagnosed with BC with SLNB indication from January 2013 to December 2015 in a single BC reference treatment institution, the Cancer Hospital III, belonging to the Brazilian National Cancer Institute (HCIII/INCA). The following exclusion criteria were considered: bilateral BC, inflammatory breast carcinoma, non-epithelial tumors, occult breast carcinoma, pregnant women, history of previous cancer, cancer treatment prior to enrollment in the hospital unit, 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 NAC.

Data were collected from physical and electronic medical records, using an instrument created specifically for this purpose. The following groups of variables were collected:

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

Clinical: alcoholism and smoking according to medical record data, 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. From this 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, using central tendency (mean) and dispersion (standard deviation) measures for continuous variables and absolute and relative frequency distributions for categorical variables. The chi-square test was carried out to compare the frequency distribution of the obtained demographic and clinical characteristics according to the axillary approach (SLNB or 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 univariate logistic regression was implemented using the crude odds ratio (OR) to assess independent factors associated with SLNB indication. 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) version 23.0 software was used for all statistical analyses.

This study was approved by the INCA Research Ethics Committee (CEP) under CAAE no. 06794512.3.00005274.

# Results

During the study period, 3,211 women were enrolled for BC treatment at the HC III/INCA. Of these, 11.9% presented a clinical staging IV and 53.7% were not submitted to NAC. The physical records of the 1,106 eligible women were consulted, and 188 women were then excluded for not meeting the eligibility criteria. The final number of patients evaluated herein comprised 918 women treated by NAC, 161 (17.5%) of whom underwent SLNB, 105 (11.4%) who underwent SLNB followed by AL and 652 (71.0%) who underwent LA only (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 elderly (≥65 years old). Most reported living without a partner (58.7%) and having studied for over eight years (56.8%). Regarding skin color, the patients were mostly non-white (65.5%) and were more frequently submitted to SLNB (72.2%) compared to white women (27.8%) (p=0.009). A statistically significant difference in SLNB performance was observed according to main patient occupation, in which 38.1% of the patients with no current external occupation (retired, pensioner, housewife and unemployed) and 61.9% of those presenting a work occupation were submitted to this procedure (p = 0.013) (Table 1).

Considering comorbidities, 372 (40.5%) of the patients presented systemic arterial hypertension and 106 (11.5%), diabetes. When applying the CCI, 86.7% exhibited no comorbidities. A higher SLNB frequency was observed in women presenting no systemic arterial hypertension (p=0.041) and no 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). Regarding molecular subtype, most patients were classified as luminal A (17.8%) and luminal B (52.2%), with no SLNB frequency difference in relation to this variable.

The average time between the last NAC cycle and surgery was 70 days (± 39) and was longer among patients submitted to SLNB (p<0.001). Regarding breast surgery, SLNB was performed more frequently 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 were previously submitted to SLNB in 11 of these cases, (p<0.001). Adjuvant treatment was applied in 96.8% of the patients by 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).

To assess factors associated with SLNB after NAC, demographic, clinical and tumor variables with p <0.20 (Tables 1 to 3) in the univariate analysis were selected for inclusion in the multiple logistic regression model. 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, the more advanced the clinical stage, the less the chance of undergoing an SLNB. In comparison with patients in stage I, women in stage III had a 95% lower chance of undergoing SLNB

(OR= 0.05 95% CI 0.01-0.17; p <0.001). Women who underwent mastectomies presented a 90% lower chance of undergoing SLNB compared to those who underwent conservative surgeries (95% CI 0.06-0.17; p<0.001). Considering NAC responses, cases with no response or presenting disease progression exhibited a 55% lower chance 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 in the treatment of BC. Those at a more advanced clinical stage with a worse response to NAC, and those who underwent mastectomies were less likely to undergo SLNB.

The studied population displayed a mean age of 51.58 years old, similar to other series of BC patients who underwent NAC [13-16]. 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 [14,15].

Most women had brown skin color (47.7%), followed by white (34.1%) and black (17.5%). The highest percentage of brown skin color, when considered as a socioeconomic level proxy, may reflect greater medical care access difficulty, 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 [17-21]. It is important to note that this data is self-reported in this study, which can make it difficult to characterize this variable, as well as the high Brazilian population miscegenation.

Among molecular cancer subtypes, luminal B corresponded to 52.2% of the cases, followed by triple-negative at 19.1%, luminal A at 17.8 % and HER2 at 7.8%. In Brazil, luminal subtype B is the most frequent subtype [16,22,23]. However, different incidences between the five regions of the country are noted. In the Southeast region, this type corresponds to 39. % of cases, followed by luminal A at 28.8 %, triple-negative at 14.0% and HER2 at 7.9% [24]. In other populations submitted to NAC, the luminal molecular subtype B has been reported as the most frequent [25,26]. In a cohort of 601 patients aiming to describe the immunohistochemical profile of BC, Cintra *et al.* [22] observed that, in stage III, most patients comprised luminal subtype B, at 53.1% of the assessed cases, followed by triple-negative, at 35.9% of all cases. Luminal subtype A is a tumor subtype associated with lower aggression, earlier stage tumors and less response to NAC, as well as higher false-negative results in SLNB, which could explain the lower frequency of its indication in patients undergoing NAC [22,27]. 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 NAC indication.

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 [28]. In our 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 so most of the time after NAC. In this study, 62.0% of patients classified as cN0 were negative by the histopathological examination (ypN0), while 38.0% displayed a positive result (ypN1). Galimberti et al. [29] reported that, out 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 a lower cN and a greater complete pathological response (PRC) concerning the armpit (66.5% x 33.1%) compared to those submitted to AL [15].

The present study did not include clinical axillary assessments after NAC, which limits exam accuracy evaluations, 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%, that the rate of false-negative results was 82% and the positive predictive value was 89%, demonstrating that the accuracy of the physical axillary examination after NAC is of 45% [30].

In addition, in patients with an 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 patients (62.9%), with 37.1% negative. The literature demonstrates that the conversion of positive (cN1) to negative (ypN0) axillary nodes is of 28% [30]. This may indicate that, in addition to axillary node response, an overestimation if the axillary clinical evaluation in this study may have occurred.

Mastectomy was the most frequent surgery, carried out in in 82.7% of cases. Even in patients presenting an indication for SLNB, mastectomy occurred in 53.0% of cases. This is compatible with the study's the complete response rate of 13.5% and partial response of 63.6%. The literature demonstrates that, despite the increases in response in NAC, this is not translated into an increase in conservative surgeries as would be expected [31]. While, response rates around 30% to 40% are observed for some subtypes, the rate of reduction in mastectomies in some series is of around 17%. This fact can be partly explained by the presence of extensive intraductal components, the possibility of poor aesthetic results, the surgeon's experience and the patients' desire [31].

In the present study, advanced disease characteristics were associated with SLNB in the adjusted model. In comparison with stage I, patients at stage III were 95% less likely to be submitted to SLNB, regardless of their NAC response, as demonstrated by the multiple regression model. Likewise, the worse response, the lower the chance of SLNB. Cases that did not present response in NAC exhibited a 55% lower chance 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 [15].

This study presents certain limitations that may compromise its internal validity, including as observational design, comprising retrospective data collection. Among possible biases, we highlight the

low effect magnitudes obtained in some association measures. 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, the fact that the data were obtained by an active medical record search may have introduced a classification bias. Similarly, the absence of certain clinical variables, such as physical examinations performed after NAC, could serve as adjustment variables and were not obtained. Performing immunohistochemistry on sentinel lymph nodes after NAC can also provide more accurate information on the existence of residual axillary disease. However, during the period in which the patients were included in the study, this examination 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, presented 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 posterior surgical indication, regardless of 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 potential of this study comprises the real-life evaluation, of a high number of women with homogeneous characteristics and the presentation of safe results concerning SLNB performance after NAC, which may result in decreased morbidity and lethality rates, thus improving the assistance provided to this population.

# Conclusions

In the present study, SLNB was performed after NAC in 29% of the evaluated 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.

# Declarations


### FUNDING

Not applicable


### conflicts of interest

The authors declare no conflict of interest

### Availability of data and material

Data available on request due to privacy/ethical restrictions

### Code availability

Not applicable

### Authors' contributions

Marcelo Adeodato Bello: Author make substantial contributions to conception and design, analysis and interpretation of data, participate in drafting the article, and give final approval of the version to be submitted and any revised version.

Anke Bergmann: Author make substantial contributions to conception and design, analysis and interpretation of data, participate in drafting the article and give final approval of the version to be submitted and any revised version.

Suzana Sales de Aguiar: Author make substantial contributions to acquisition of data, and interpretation of data, participate in revising it critically for important intellectual content and give final approval of the version to be submitted and any revised version.

Marcelo Morais Barbosa: Author make substantial contributions to acquisition of data, and interpretation of data, participate in revising it critically for important intellectual content and give final approval of the version to be submitted and any revised version.

Emanuelle Narciso Alvarez Valente: Author make substantial contributions to acquisition of data, and interpretation of data, participate in revising it critically for important intellectual content and give final approval of the version to be submitted and any revised version.

Luiz Claudio Santos Thuler: Author make substantial contributions to conception and design, analysis and interpretation of data, participate in revising it critically for important intellectual content and give final approval of the version to be submitted and any revised version.

### Ethics approval

This study was approved by the INCA Research Ethics Committee (CEP) under CAAE no. 06794512.3.00005274.

## References


1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 68(6), 394–424. https://doi.org/10.3322/caac.21492.
2. INSTITUTO NACIONAL DE CÂNCER JOSÉ ALENCAR GOMES DA SILVA. **Estimativa 2020**: Incidência de Câncer no Brasil. Rio de Janeiro: INCA, 2019. https://www.inca.gov.br/publicacoes/livros/estimativa-2020-incidencia-de-cancer-no-brasil
3. Mano, MS. Neoadjuvant chemotherapy in breast cancer: time for an appraisal. (2018) Mastology, 28(3):131-3. https://doi.org/10.29289/259453942018EDIT283.

4. Spring, L., Greenup, R., Niemierko, A., Schapira, L., Haddad, S., Jimenez, R., Coopey, S., Taghian, A., Hughes, K. S., Isakoff, S. J., Ellisen, L. W., Smith, B. L., Specht, M., Moy, B., & Bardia, A. (2017). Pathologic Complete Response After Neoadjuvant Chemotherapy and Long-Term Outcomes Among Young Women With Breast Cancer. Journal of the National Comprehensive Cancer Network : JNCCN, 15(10), 1216–1223. https://doi.org/10.6004/jnccn.2017.0158
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2018). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. The Lancet. Oncology, 19(1), 27–39. https://doi.org/10.1016/S1470-2045(17)30777-5
6. Lee, S. B., Yu, J. H., Park, H., Kim, H. J., Park, S. H., Chae, B. J., Youn, H. J., Jung, S. Y., Kim, E. K., Jung, Y. S., & Son, B. H. (2019). Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer with axillary node metastasis: A survey of clinical practice. Asian journal of surgery, 42(1), 314–319. https://doi.org/10.1016/j.asjsur.2018.06.004
7. Magnoni, F., Galimberti, V., Corso, G., Intra, M., Sacchini, V., & Veronesi, P. (2020). Axillary surgery in breast cancer: An updated historical perspective. Seminars in oncology, 47(6), 341–352. https://doi.org/10.1053/j.seminoncol.2020.09.001.
8. Wazir, U., & Mokbel, K. (2020). De-escalation of Axillary Surgery in the Neoadjuvant Chemotherapy (NACT) Setting for Breast Cancer: Is it Oncologically Safe?. Anticancer research, 40(10), 5351–5354. https://doi.org/10.21873/anticanres.14542
9. Boughey, J. C., Suman, V. J., Mittendorf, E. A., Ahrendt, G. M., Wilke, L. G., Taback, B., Leitch, A. M., Flippo-Morton, T. S., Kuerer, H. M., Bowling, M., Hunt, K. K., & Alliance for Clinical Trials in Oncology (2015). Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). Annals of surgery, 261(3), 547–552. https://doi.org/10.1097/SLA.0000000000000551
10. Boileau, J. F., Poirier, B., Basik, M., Holloway, C. M., Gaboury, L., Sideris, L., Meterissian, S., Arnaout, A., Brackstone, M., McCready, D. R., Karp, S. E., Trop, I., Lisbona, A., Wright, F. C., Younan, R. J., Provencher, L., Patocskai, E., Omeroglu, A., & Robidoux, A. (2015). Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 33(3), 258–264. https://doi.org/10.1200/JCO.2014.55.7827
11. Derks, M., & van de Velde, C. (2018). Neoadjuvant chemotherapy in breast cancer: more than just downsizing. The Lancet. Oncology, 19(1), 2–3. https://doi.org/10.1016/S1470-2045(17)30914-2.
12. Gandhi, A., Coles, C., Makris, A., Provenzano, E., Goyal, A., Maxwell, A. J., & Doughty, J. (2019). Axillary Surgery Following Neoadjuvant Chemotherapy - Multidisciplinary Guidance From the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology. Clinical oncology (Royal College of Radiologists (Great Britain)), 31(9), 664–668. https://doi.org/10.1016/j.clon.2019.05.021

13. Caudle, A. S., Yu, T. K., Tucker, S. L., Bedrosian, I., Litton, J. K., Gonzalez-Angulo, A. M., Hoffman, K., Meric-Bernstam, F., Hunt, K. K., Buchholz, T. A., & Mittendorf, E. A. (2012). Local-regional control according to surrogate markers of breast cancer subtypes and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast conserving therapy. Breast cancer research : BCR, 14(3), R83. https://doi.org/10.1186/bcr3198
14. Rosenberger, L. H., Ren, Y., Thomas, S. M., Greenup, R. A., Fayanju, O. M., Hwang, E. S., & Plichta, J. K. (2020). Axillary lymph node dissection in node-positive breast cancer: are ten nodes adequate and when is enough, enough?. Breast cancer research and treatment, 179(3), 661–670. https://doi.org/10.1007/s10549-019-05500-9
15. Srour, M. K., Tseng, J., Luu, M., Alban, R. F., Giuliano, A. E., & Chung, A. (2019). Patterns in the Use of Axillary Operations for Patients with Node-Positive Breast Cancer After Neoadjuvant Chemotherapy: A National Cancer Database (NCDB) Analysis. Annals of surgical oncology, 26(10), 3305–3311. https://doi.org/10.1245/s10434-019-07540-3.
16. Amendola, L. C. B., Gaui, M. F. D., Carneiro, A. H. P. C., Canedo, N. H. S. (2021). Clinicopathologic profile of breast cancer patients treated with neoadjuvant chemotherapy at HUCFF/UFRJ. Mastology 2021;31:e20200076. https://doi.org/10.29289/2594539420200076.
17. Rocha-Brischiliari, S. C., Andrade, L., Nihei, O. K., Brischiliari, A., Hortelan, M., Carvalho, M., & Pelloso, S. M. (2018). Spatial distribution of breast cancer mortality: Socioeconomic disparities and access to treatment in the state of Parana, Brazil. PloS one, 13(10), e0205253. https://doi.org/10.1371/journal.pone.0205253
18. Renna Junior, N. L., & Silva, G. (2018). Late-Stage Diagnosis of Breast Cancer in Brazil: Analysis of Data from Hospital-Based Cancer Registries (2000–2012). Diagnóstico de câncer de mama em estado avançado no Brasil: análise de dados dos registros hospitalares de câncer (2000–2012). Revista brasileira de ginecologia e obstetricia Revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia, 40(3), 127–136. https://doi.org/10.1055/s-0038-1624580
19. Ko, N. Y., Hong, S., Winn, R. A., & Calip, G. S. (2020). Association of Insurance Status and Racial Disparities With the Detection of Early-Stage Breast Cancer. JAMA oncology, 6(3), 385–392. https://doi.org/10.1001/jamaoncol.2019.5672
20. Mets, E. J., Chouairi, F. K., Gabrick, K. S., Avraham, T., & Alperovich, M. (2019). Persistent disparities in breast cancer surgical outcomes among hispanic and African American patients. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 45(4), 584–590. https://doi.org/10.1016/j.ejso.2019.01.016
21. Hardy, D., & Du, D. Y. (2020). Socioeconomic and Racial Disparities in Cancer Stage at Diagnosis, Tumor Size, and Clinical Outcomes in a Large Cohort of Women with Breast Cancer, 2007–2016. Journal of racial and ethnic health disparities, 10.1007/s40615-020-00855-y. Advance online publication. https://doi.org/10.1007/s40615-020-00855-y
22. Cintra, J. R. D., Teixeira, M. T. B, Diniz, R. W., Gonçalves Junior, H., Florentino, T. M., Freitas, G. F., Oliveira, L., R., M., Neves, M., T., R., Pereira, T., Guerra, M. R. (2012). Perfil imuno-histoquímico e

variáveis clinicopatológicas no câncer de mama. Revista da Associação Médica Brasileira, 58(2), 178–187. https://doi.org/10.1590/S0104-42302012000200013.

23. Soares, I., Bello, M. A., Bergmann, A., & Thuler, L. (2021). Comparison of the performance of four staging systems in determining the prognosis of breast cancer among women undergoing neoadjuvant chemotherapy. Breast cancer research and treatment, 10.1007/s10549-020-06077-4. Advance online publication. https://doi.org/10.1007/s10549-020-06077-4
24. Carvalho, F. M., Bacchi, L. M., Pincerato, K. M., Van de Rijn, M., & Bacchi, C. E. (2014). Geographic differences in the distribution of molecular subtypes of breast cancer in Brazil. BMC women's health, 14, 102. https://doi.org/10.1186/1472-6874-14-102.
25. Blanco Sánchez A, Yébenes L, Berjón A, Hardisson D. (2021). Evaluation of pathological response to neoadjuvant chemotherapy in breast cancer: correlation with molecular phenotype. Rev Esp Patol; 54(1):8–16. https://doi.org/doi: 10.1016/j.patol.2020.07.003.
26. Kunnuru, S., Thiyagarajan, M., Martin Daniel, J., & Singh K, B. (2020). A Study on Clinical and Pathological Responses to Neoadjuvant Chemotherapy in Breast Carcinoma. Breast cancer (Dove Medical Press), 12, 259–266. https://doi.org/10.2147/BCTT.S277588.
27. Enokido, K., Watanabe, C., Nakamura, S., Ogiya, A., Osako, T., Akiyama, F., Yoshimura, A., Iwata, H., Ohno, S., Kojima, Y., Tsugawa, K., Motomura, K., Hayashi, N., Yamauchi, H., & Sato, N. (2016). Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in Patients With an Initial Diagnosis of Cytology-Proven Lymph Node-Positive Breast Cancer. Clinical breast cancer, 16(4), 299–304. https://doi.org/10.1016/j.clbc.2016.02.009
28. Giuliano, A. E., Ballman, K. V., McCall, L., Beitsch, P. D., Brennan, M. B., Kelemen, P. R., Ollila, D. W., Hansen, N. M., Whitworth, P. W., Blumencranz, P. W., Leitch, A. M., Saha, S., Hunt, K. K., & Morrow, M. (2017). Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA, 318(10), 918–926. https://doi.org/10.1001/jama.2017.11470
29. Galimberti, V., Ribeiro Fontana, S. K., Maisonneuve, P., Steccanella, F., Vento, A. R., Intra, M., Naninato, P., Caldarella, P., Iorfida, M., Colleoni, M., Viale, G., Grana, C. M., Rotmensz, N., & Luini, A. (2016). Sentinel node biopsy after neoadjuvant treatment in breast cancer: Five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 42(3), 361–368. https://doi.org/10.1016/j.ejso.2015.11.019
30. Caudle, A. S., Kuerer, H. M., Krishnamurthy, S., Shin, K., Hobbs, B. P., Ma, J., Mittendorf, E. A., Washington, A. C., DeSnyder, S. M., Black, D. M., Hunt, K. K., & Yang, W. T. (2019). Feasibility of fine-needle aspiration for assessing responses to chemotherapy in metastatic nodes marked with clips in breast cancer: A prospective registry study. Cancer, 125(3), 365–373. https://doi.org/10.1002/cncr.31825
31. Moo, T. A., Edelweiss, M., Hajiyeva, S., Stempel, M., Raiss, M., Zabor, E. C., Barrio, A., & Morrow, M. (2018). Is Low-Volume Disease in the Sentinel Node After Neoadjuvant Chemotherapy an Indication

for Axillary Dissection?. Annals of surgical oncology, 25(6), 1488–1494. https://doi.org/10.1245/s10434-018-6429-2.

# Tables

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 | | |
|---|---|---|---|---|
| | | AL (n = 652) N (%)* | SLNB (n = 266) N (%)* | P value** |
| 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) | 0.122 |
| 40–64 years | 656 (71.5) | 475 (72.9) | 181 (68.0) | |
| ≥ 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 | | | | |
| living with a partner | 370 (40.3) | 254 (39.4) | 116 (43.8) | 0.227 |
| Living without a partner | 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 external occupation | 280 (30.5) | 206 (48.9) | 74 (38.1) | 0.013 |
| Work occupation | 335 (36.5) | 215 (51.1) | 120 (61.9) | |
| Missing | 303 (33.0) | | | |
| Alcohol consumption | | | | |

| Variables | Total N (%) | Axillary approach | | |
|---|---|---|---|---|
| | | AL (n = 652) N (%)* | SLNB (n = 266) N (%)* | P value** |
| No | 661 (72.0) | 466 (76.4) | 195 (76.8) | 0.623 |
| Yes (occasional or frequent) | 188 (20.5) | 135 (22.1) | 53 (20.9) | |
| Ex-consumer | 15 (1.6) | 09 (1.5) | 06 (2.4) | |
| Missing | 54 (5.9) | | | |
| Tabaco consumption | | | | |
| No | 616 (67.1) | 442 (72.2) | 174 (68.0) | 0.208 |
| Yes (occasional or frequent) | 252 (29.0) | 170 (27.8) | 82 (32.0) | |
| 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 |
| Status nutritional | | | | |
| Low or normal weight (< 24.9) | 242 (26.4) | 172 (26.5) | 70 (26.3) | 0.713 |
| Pre-obesity (25.0 to 29.9) | 341 (37.1) | 237 (36.5) | 104 (39.1) | |
| Obesity (≥ 30) | 333 (36.3) | 241 (37.1) | 92 (34.6) | |
| Missing | 02 (0.2) | | | |

| Variables | Total N (%) | Axillary approach | | |
|---|---|---|---|---|
| | | AL (n = 652) N (%)* | SLNB (n = 266) N (%)* | P value** |

SD = Standard deviation; AL = axillary lymphadenectomy; SSLNB = 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 | | | |
|---|---|---|---|---|---|
| | | AL (n = 652) (A) N (%)* | SLNB (n = 266) (B) N (%)* | P value** | Z Test *** |
| 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 |

| Variables | Total N (%) | Axillary approach | | | |
|---|---|---|---|---|---|
| | | AL (n = 652) (A) N (%)* | SLNB (n = 266) (B) N (%)* | P value** | Z Test *** |
| 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) | | | | |

| Variables | Total N (%) | Axillary approach | | | |
|---|---|---|---|---|---|
| | | AL (n = 652) (A) N (%)* | SLNB (n = 266) (B) N (%)* | P value** | Z Test *** |
| 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) | | | | |

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 3 or more categories.

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

| Variables | Total N (%) | Axillary approach | | |
|---|---|---|---|---|
| | | AL (n = 652) N (%)* | SLNB (n = 266) N (%)* | P value** |
| 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) | |

| Variables | Total N (%) | Axillary approach | | |
|---|---|---|---|---|
| | | AL (n = 652) N (%)* | SLNB (n = 266) N (%)* | P value** |

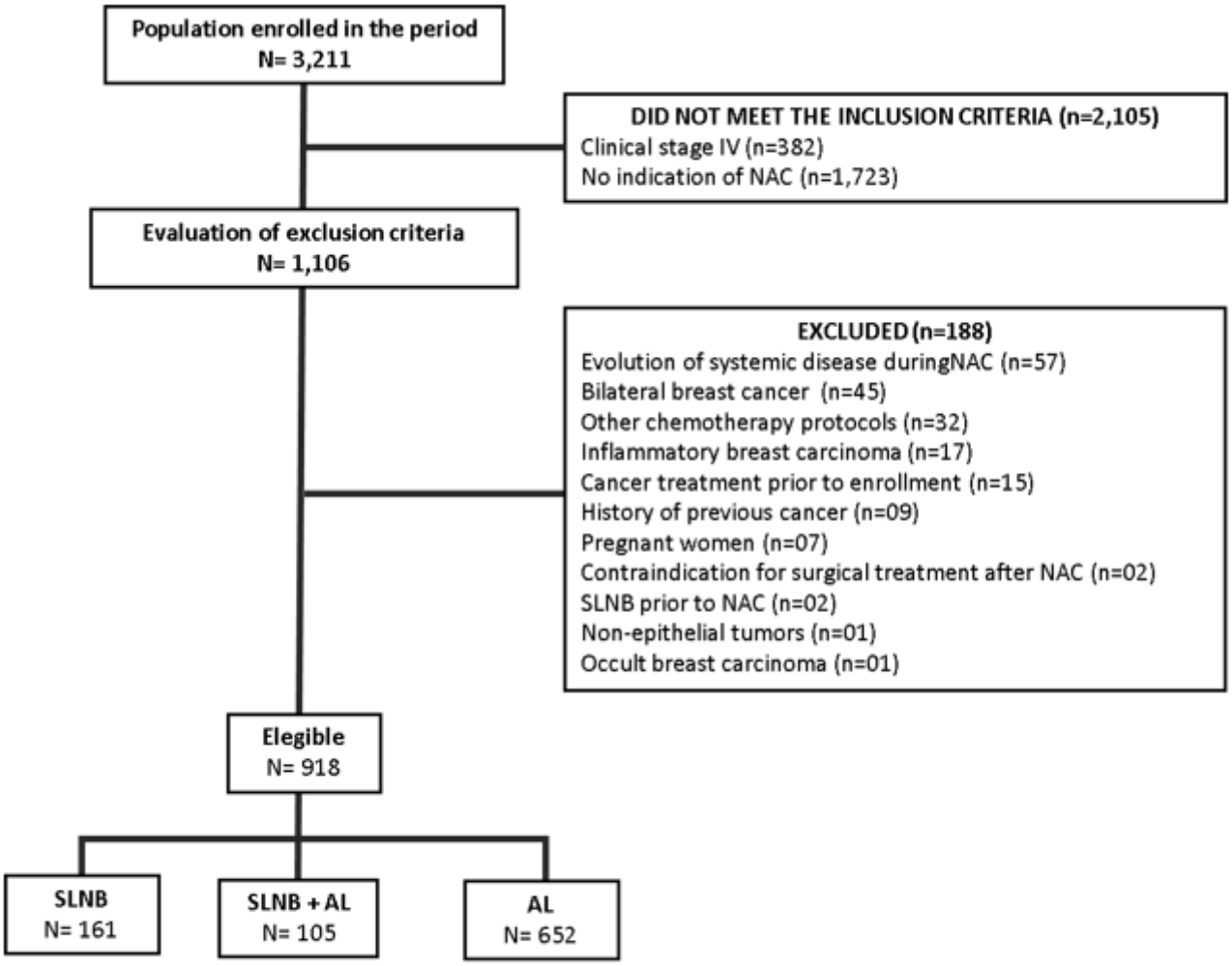
NAC = neoadjuvant chemotherapy; SD = Standard deviation; AL = axillary lymphadenectomy; SLNB = sentinel lymph node biopsy. * Percentage in columns; ** Calculated with known values.

Table 4
– Multiple logistic regression to assess factors associated with sentinel lymph node biopsy indication and independent variables (n = 918).

| Variável | 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 external occupation | Reference | 0.013 | — | — |
| Work occupation | 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) | | | | |

| Variável | Univariate | | Multiple (adjusted) | |
|---|---|---|---|---|
| | Crude OR (95% CI) | P value* | Adjusted OR (95% CI) | P value* |
| 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 a | Reference a | < 0.001 | Reference | < 0.001 |
| Conservative surgery | 0.06 (0.04–0.09) | | 0.10 (0.06–0.17) | |
| OR = Odds ratio; NAC = neoadjuvant chemotherapy; CI = Confidence interval. | | | | |

# Figures




## Figure 1

Flowchart of identification of study patients