


Axillary management for patients with breast cancer after neoadjuvant chemotherapy: Results of a survey among Brazilian breast surgeons

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Abstract

Background: Currently, there are broadly differing patterns in the management of the axilla after neoadjuvant chemotherapy (NAC) and no consensus with clinically strong evidence on the subject. A survey was performed to assess the current axillary management after NAC among Brazilian breast cancer surgeons.

Methods: The Brazilian Society of Mastology members were invited by email to complete an anonymous online survey and a total of 426 responses were collected.

Results: The majority of responders (67%) indicated performing routine axillary staging by physical exam, ultrasound, and fine needle biopsy in case of a suspicious node before NAC. Among breast surgeons working in the Brazilian Public Unified Health System, 11.3% answered that sentinel lymph node biopsy (SLNB) is not reasonable after NAC in their services. Seventy-seven responders (18.2%) reported performing SLNB instead of axillary lymph node dissection (ALND) only in patients who are clinically node-negative before NAC. Axillary complete pathologic response is necessary to omit ALND for 42.8% of responders. The molecular profile of a breast tumor is not considered when choosing axillary management after NAC for 73.7% of responders.

Conclusions: Our survey highlighted the trend towards de-escalation of axillary surgery and observed high heterogeneity in axillary management after chemotherapy in a group of Brazilian breast surgeons.

KEYWORDS

breast neoplasm, neoadjuvant therapy, sentinel lymph node

1 | INTRODUCTION

Neoadjuvant chemotherapy (NAC) is increasingly administered to women with breast cancer and currently applied to decrease tumor size, allowing breast-conserving surgery instead of mastectomy and also reverting inoperable tumors into operable ones.^{1,2} Although, de-escalation of breast

surgery is a reality in patients with early-stage breast cancer minimizing surgery morbidity and increasing quality of life,³ axillary conservative management in the era of NAC remains controversial.⁴ The identification of negative lymph nodes in a patient with cN1 disease at diagnosis might be difficult using sentinel lymph node biopsy (SLNB) after NAC, the false-negative rates of SLNB being one of the main concerns. Identification of

residual nodal disease after NAC can provide an opportunity to participate in adjuvant trials with potential benefits to tailor adjuvant treatment and improve survival, at least in HER2 positive and triple-negative (TN) breast cancer.^{5,6} Different authors have been showing the efficacy of SLNB to assess axillary response in patients who underwent neoadjuvant treatment^{7,8} encouraging the use of SLNB instead of ALND in breast cancer patients with a pathological complete response to NAC. The ACOSOG Z1071 clinical trial and The European SENTinel NeoAdjuvant (SENTINA) trial demonstrated a high false-negative rate (FNR) for SLNB after NAC in patients with cN1 breast cancer, which decreased to an acceptable rate when removing three or more lymph nodes with dual tracer mapping.^{7,8} Galimberti et al⁹ showed an overall survival of 86.3% in initially cN1/N2 patients before NAC and sentinel node-negative after NAC after a median follow-up of 61 months. Consequently, surgeons are offering SLNB instead of ALND in clinical negative axillary staging after NAC. There is still a lack of reliable long-term data about outcomes and no consensus on which procedure is the most accurate for axillary staging after NAC.

This survey was designed to highlight the reality in Brazilian clinical practice in assessing the management of axilla after NAC among breast surgeons.

2 | METHODS

An anonymous survey was sent to members of the Brazilian Society of Mastology, conducted over a 2-month period. The Brazilian Society of Mastology members were invited by email to participate in a study with a link to six questions (Table 1). The survey was developed using SurveyMonkey Inc. and the main focus of the questions was surgeon knowledge and practice in axillary management after NAC.

The answers were multiple choice alternatives in all of six questions. The results were summarized as percentages and showed in graphs based on the total number of responders to each question.

3 | RESULTS

3.1 | Axillary staging before NAC

Overall, 426 responses (21.3%) of 2000 eligible members were collected by breast surgeon members of the Brazilian Society of Mastology.

The first question was about the methods recommended as a routine axilla evaluation in patients who are to undergo NAC. Almost half of the responders (43.4%, n = 184) reported routine axillary staging by physical exam, including ultrasound and fine needle biopsy (FNB), if necessary. Adding a metallic clip to the biopsied lymph node was chosen by 23.7% (n = 101) of responders, followed by physical exam plus axillary ultrasound in 17.2% of the responses (n = 73) and only physical exam in 15.7% of the responses (n = 67).

3.2 | Axillary surgery after NAC in the public health system: Is SLNB reasonable?

We asked the physicians working on the Brazilian Unified Health System if they perform SLNB in patients submitted to NAC, 59.7% (n = 254) responded yes while 11.3% (n = 48) opt for axillary dissection. Almost a third of responders (29.2%, n = 124) reported not working in the Brazilian Unified Health System and could not respond to the question.

3.3 | Considering performing SLNB after NAC in cN0, cN1, cN2, and cN3

A total of 424 participants reported their practice of axillary assessment after NAC. The omission of ALND in clinically positive axilla patients undergoing NAC getting a complete clinical and radiological response (documented by radiological methods—not specified which methods in question), depending on the axillary staging before

TABLE 1 Questions of survey

Questions	Responders
Q1. Which methods of diagnosis would you recommend as a routine axilla evaluation in patients who are to undergo neoadjuvant chemotherapy?	425
Q2. Is the biopsy of sentinel lymph node after neoadjuvant chemotherapy a reality where you work? Consider only services linked to the Brazilian Unified Health System.	426
Q3. Would you recommend/perform the biopsy of sentinel lymph node as opposed to axillary dissection after neoadjuvant chemotherapy in the following situation?	424
Q4. For which clinical stage before chemo with a complete clinical and radiologic response after chemo would you recommend a sentinel lymph node biopsy?	426
Q5. In which scenario would you NOT recommend an axillary dissection (lymphadenectomy) after sentinel lymph node biopsy?	421
Q6. Is the molecular profile of a tumor a fact that influences a decision whether to perform a biopsy of the sentinel lymph or an axillary dissection in a clinically positive axilla patient who had a full radiologic and clinical complete response after neoadjuvant chemotherapy?	426

chemotherapy was reported by 211 participants (49.8%). Almost one-third, 32.1% (n = 136) responded that they did not consider the axillary involvement level (N1 vs N2 vs N3) before NAC to decide using SLND instead of ALND, therefore they perform SLND in patients getting a complete response, regardless of the axillary involvement level. Seventy-seven responders (18.2%) reported performing SLND instead of ALND only in patients who are clinically node-negative before NAC.

3.4 | Sentinel node biopsy after NAC with complete image and clinical response

The following question evaluated specifically the axillary level involvement before NAC in patients with clinically complete responses. All participants (n = 426) fully answered this question, 11% perform only SLNB instead of ALND in patients with no axillary involvement, 42.5% (n = 181) in patients diagnosed with N1, 27.7% (n = 118) in N1 and N2 and 18.8% (n = 118) in N1, N2, and N3 (Figure 1).

3.5 | Avoiding axillary dissection with positive SLNB after NAC

One hundred and seventy-eight (42.8%) responders reported that an axillary complete pathologic response (ypN0) is necessary to omit ALND and 19.5% (n = 82) do not perform ALND in patients with ypN1is+ (isolated tumor cells). Considering the patients with ypN1is+ (isolated tumor cells) and ypN1mic (micrometastasis), 24.5% (n = 103) reported not performing ALND after SLND. Fifty-eight participants (13.8%) accepted omitting ALND after SLND in patients with ypN1is+ (isolated tumor cells), ypN1mic (micrometastasis), and ypN1 (Figure 2).

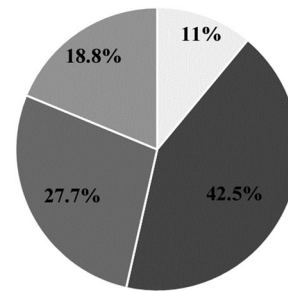
3.6 | Molecular profiling influencing SLNB after NAC in cN positive before NAC

Lastly, we asked about the molecular profile influencing ALND vs SLNB decision in breast cancer patients getting an axillary complete pathological response after NAC. All 426 participants responded to the question, 63.7% (n = 314) do not consider molecular profiling when choosing axillary management after NAC, and for 26.3% (n = 112) of responders, the breast cancer molecular profile influence the decision.

4 | DISCUSSION

The trend towards less-invasive axillary surgery after NAC is a reality in Brazil for most breast surgeons who responded to the survey, with 89% considering performing SLNB after NAC in patients diagnosed with clinically positive nodes before systemic

Q1- For which clinical stage prior to chemotherapy with complete clinical and radiologic response after NAC would you recommend SLNB?



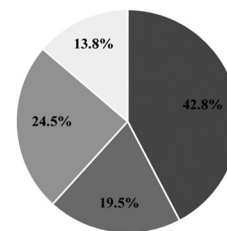
■ Only in N0 ■ N0 and N1 ■ N0, N1 and N2 ■ N0, N1, N2 and N3

FIGURE 1 Sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NAC) with complete response

treatment. The Brazilian Unified Health System is a public and complex system that still presents with different levels of access to assistance in the geographic areas in Brazil. Understanding how patients are treated in this system is really important as 76% of the Brazilian population are covered only by this health care system.^{10,11} We also observed that almost 16% of surgeons working in the public health system opt for ALND after NAC because SLNB is not suitable in their hospitals. In Brazil, it is important to consider that not all hospitals have specialized pathologists to perform transoperative freezing, tecnesio to make a double tracer or metallic clip to insert in suspicious biopsied nodes. These discrepancies can interfere with the results of the survey.

Our survey highlighted the heterogeneity of axillary management after NAC in Brazilian practice. The majority of breast surgeons (43.4%) responded to performing routine axillary staging by physical exam, ultrasound and fine needle biopsy (FNB) (if suspicious node) in patients who were to undergo NAC, while fewer responses include adding a metallic clip to the biopsied node as a routine axilla evaluation in these patients. Although the insertion of the clip is not

Q2- In which scenario would you NOT recommend an axillary dissection after SLNB?



■ ypN0
 ■ ypN0 e ypN1is+ (isolated tumor cells)
 ■ ypN0, ypN1is+ (isolated tumor cells) and ypN1mic (micrometastases)
 ■ ypN0, ypN1is+ (isolated tumor cells) and ypN1mic (micrometastases) and ypN1

FIGURE 2 Avoiding axillary dissection with positive sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NAC)

fully accepted, some surgeons cannot even consider this possibility because metallic clips are not available in all hospitals and clinics.^{12,13}

As expected, the axillary staging before chemotherapy was the main factor to consider the omission of ALND in clinically positive axilla patients undergoing NAC getting a complete clinical response. What was not expected was the high number of breast surgeons that responded to not considering the axillary involvement level (N1/N2/N3) before NAC to decide on using SLNB instead of ALND. Most of the responders (42.5%) perform SLNB instead of ALND in patients with N1 axillary involvement before NAC, however, many breast surgeons also indicated SLNB for N2 (27.7%) and N3 (18.8%) patients. This result was unexpected, as we presumed higher rates of breast surgeons performing SLNB in only cN1 patients based on previous literature. Boughey et al¹⁴ showed in the ACOSOG Z1071 study, a decreased FNR when two or more sentinel lymph nodes (SLNs) were examined in cN1 patients undergoing NAC (n = 34), however, they excluded cN2 disease from the primary analysis. In the SENTINA trial, the authors did not assess cN1 and cN2 separately, and Galimberti and colleagues^{8,9} also demonstrated the overall survival rates of SLNB after NAC in patients cN1 and cN2 together. None of the trials included cN3 patients.

The Brazilian Society of Mastology developed a guideline in a consensus conference to optimize clinical practice for breast cancer patients that undergo neoadjuvant therapy. About axillary management after NAC, the panel considered NAC acceptable in chemoresponsive subtypes and as a strategy to avoid axillary dissection, in node-positive patients who convert to clinically node-negative after NAC. Corroborating the medical literature, the panel considered the biopsy of an NO lymph node after the NAC a safe procedure. They also confirmed the safety of SLNB for initially N1 patients that became NO after neoadjuvant treatment.¹⁵ An analysis of the national cancer database demonstrated an increased number of SLNB in breast cancer patients with positive lymph node undergoing NAC between 2012 and 2015.¹⁶ When considering the scenario in which surgeons do not perform ALND after SLNB, the majority (42.8%) responded that an axillary complete pathologic response (ypN0) is really necessary to omit ALND. However, many responders also do not perform ALND in patients with ypN1is+ (isolated tumor cells) and ypN1mic (micrometastasis). These options include patients with clinically radiologic remission but not complete pathologic response. On the basis of the clinical data, the Brazilian Society of Mastology consensus recommends axillary dissection for patients diagnosed with micrometastasis in SLNB after neoadjuvant treatment, therefore, we were surprised that breast surgeons are omitting ALND for these patients.¹⁵ The surgical approach to the axilla in breast cancer patients undergoing neoadjuvant therapy is still controversial, and more studies are needed to clarify the best axillary management after NAC. One possible explanation to consider not performing ALND in patients with the residual disease is the patients' difficulty to return for a second surgery in some Brazilian hospitals and also the benefits of radiotherapy in axillary residual disease, already proven in different scenarios without NAC (AMAROS trial) and under

investigation for NAC in the ALLIANCE A11202 trial.^{17,18} In our survey, molecular profiling influenced the decision of SLNB instead of ALND in breast cancer patients getting an axillary complete pathological response after NAC in approximately one-third (26.3%) of the responders. A recent study showed that patients with TN and HER2+ breast tumors and clinically node-positive disease achieve higher rates of pathologic complete response (PCR) after NAC when compared to hormone receptor-positive/HER2 negative subtypes.¹⁹

Breast PCR is highly correlated with axillary PCR after NAC in HER2+ and TN disease. The risk for missing nodal metastasis in these subtypes is lower than in hormone-positive tumors and concerns about FNR or even avoiding axillary surgery might be considered for hormone-positive subtypes.^{20,21} Patients diagnosed with TN and HER2 positive tumor and clinically negative-node disease also benefit more from a de-escalation of axillary surgery after chemotherapy demonstrating lower rates of positive SLNs.^{19,22} New studies focusing on the influence of tumor molecular profiling in axilla management after NAC in Brazilian practice might better explain the knowledge of breast surgeons on the subject, and in which cases they are indicating SLNB.

Our study has a few limitations. The survey was brief and simple to optimize the number of responses. We consider 21% a satisfactory rate of responses considering the voluntary participation of the surgeons and the surgeons' tendency to being more familiar with breast cancer trials. However, sampling is a limitation of our study. We also did not have specific questions in the survey, however, our aim was not specific, we expected to confirm a previous report on how breast surgeons are indicating axillary management after NAC in Brazilian practice. Our survey can highlight possible questions to be explored in further randomized and cohort trials, however, the results not allow for recommendations or use of one specific technique for axillary management after NAC.

5 | CONCLUSION

In conclusion, our survey highlighted the trend for de-escalation of axillary surgery in patients undergoing NAC for most surgeons who responded the survey working in Brazil and also in the Brazilian Unified Health System. We also demonstrated that a high heterogeneity of axillary management after NAC still exists in Brazilian practice.

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CONFLICT OF INTERESTS

The author Antônio L. Frasson has received a speaker honorarium from Roche. Remaining authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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