






Axillary recurrence after neoadjuvant chemotherapy: a retrospective study

Lillian Maria Fernandes de Castro¹ , Marina Silva Camarço Lima¹ ,
Rafael Everton Assunção Ribeiro da Costa^{2*} , Thiago Pereira Diniz³ , Sabas Carlos Vieira⁴ 

ABSTRACT

Introduction: The justification for this study emerged from the need to evaluate the performance of axillary lymphadenectomy in patients with positive sentinel lymph nodes who underwent neoadjuvant chemotherapy. Axillary lymph node dissection is an invasive and potentially morbid procedure designed to achieve complete remission of breast cancer and prevent unnecessary radical surgery. With the omission of the axillary lymphadenectomy, surgical complications are avoided including lymphedema, stress is decreased, and the quality of life improves in these patients. This study aimed to evaluate axillary recurrence in breast cancer patients undergoing neoadjuvant chemotherapy after the omission of radical axillary lymph node dissection in patients with positive sentinel lymph nodes. **Methods:** A retrospective study was conducted with ten patients from a clinic specializing in cancer diagnosis and treatment in Teresina (PI), Brazil, diagnosed with breast cancer from January 1998 to February 2021. These patients had positive sentinel lymph nodes and did not undergo axillary node dissection after neoadjuvant chemotherapy. **Results:** The median patient age at diagnosis was 52 years. All of them had clinical axillary involvement and received neoadjuvant chemotherapy regimen with doxorubicin, cyclophosphamide, and paclitaxel. In addition, they all received adjuvant radiotherapy in the postoperative period and the mean number of sentinel lymph nodes (SLN) removed was two. At a median follow-up of 39.5 months, there was no axillary recurrence and 90% of the patients were alive. **Conclusions:** At a median follow-up of 39.5 months none of the patients presented axillary recurrence.

KEYWORDS: axilla; breast neoplasms; data analysis; lymph node excision; neoadjuvant therapy.

INTRODUCTION

The omission of axillary lymph node dissection (ALND) in patients with positive sentinel lymph nodes (SLN) following neoadjuvant chemotherapy for breast cancer remains a controversial topic with a lack of randomized clinical trials¹.

In the treatment of primary breast cancer with clinically negative axilla, a positive SLN is no longer a criterion for ALND since two randomized trials (ACOSOG Z0011 and AMAROS trial) demonstrated that there was a low axillary recurrence rate and equivalent overall survival rate when ALND was omitted and the axillary region was irradiated¹⁻⁴.

In breast cancer patients with clinically positive axilla, SLN investigation was validated in three multicenter studies. A French study of locally advanced breast tumors in patients

with clinically positive axilla, who underwent neoadjuvant chemotherapy, reported a 15% false-negative (FN) rate⁵. On the other hand, the FN rate was lower when dual tracers for SLN identification were used and at least three lymph nodes were removed⁶. Another strategy to reduce the FN rate to 2% was clip placement to mark axillary node involvement before neoadjuvant chemotherapy⁷. In contrast, a retrospective study reported that ALND should not be omitted in patients with a positive SLN after neoadjuvant chemotherapy since it determined a shorter survival rate. However, the omission of ALND did not affect survival in patients with luminal tumors that had a single SLN metastasis⁸.

While awaiting the results of a large phase III clinical trial (NCT01901094), several surgeons already omitted ALND in selected groups of patients with clinically positive axilla.

¹Centro Universitário Unifacid, Graduated in Medicine – Teresina (PI), Brazil.

²Universidade Estadual do Piauí – Teresina (PI), Brazil.

³Universidade Federal do Piauí, Hospital at the University, Oncology Surgeon – Teresina (PI), Brazil.

⁴Oncocenter, Oncology Surgeon – Teresina (PI), Brazil.

*Corresponding author: rafalearcosta@gmail.com

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In a study, it was shown that 42.8% of Brazilian breast specialists did not consider that pathologic complete response after neoadjuvant chemotherapy was a criterion for axillary clearance and 73.7% did not take the breast cancer molecular subtype into account for axillary management in this scenario⁹.

The aim of the current study was to evaluate axillary recurrence in patients with positive SLN after neoadjuvant chemotherapy, who had not undergone ALND.

METHODS

This was a retrospective case series study of breast cancer patients, conducted in the Oncocenter Clinic, Teresina (PI), Brazil. Data analysis was carried out from January 1998 to February 2021 and electronic medical records were used for the search. Patients receiving neoadjuvant chemotherapy who did not undergo radical ALND in the presence of positive sentinel lymph nodes were included in the study. Patients under 18 or over 80 years of age, those with a previous history of breast cancer treatment, and incomplete medical records were excluded.

Clinical and pathological variables, including tumor staging and treatment (surgical and systemic), were collected and shown in specific tables. The treatment decision to clear the axillary region as a result of positive SLN was made between surgeon and patient, after discussing the risks and benefits of the procedure. During surgery, a detailed axillary exploration was conducted to identify macroscopically suspicious lymph nodes. Macroscopically suspicious lymph nodes are resected intraoperatively, even when not detected by technetium or patent blue dye. All patients were operated by the same surgeon and the histopathologic report was carried out by the same team of pathologists. The research group contacted all patients to update their follow-up. Current disease status of the patient was described as alive with the disease, alive without the disease, dead from cancer, or dead due to other causes.

The study was approved on October 1, 2020, by the Research Ethics Committee of the State University of Piauí, under CAAE 30154720.0.0000.5209.

RESULTS

Figure 1 illustrates that the study population diagnosed with breast cancer was composed of 163 patients. Of the total, only ten patients who had undergone neoadjuvant chemotherapy after the omission of ALND, had SLN-positive status and fulfilled the inclusion criteria for the study.

Clinical and anatomic-pathological characteristics of the ten patients analyzed during the period are shown in Table 1.

Within a median follow-up of 39.5 months, a patient (10%) had a chest wall recurrence after mastectomy and died due to disease progression. The molecular subtype of breast cancer of

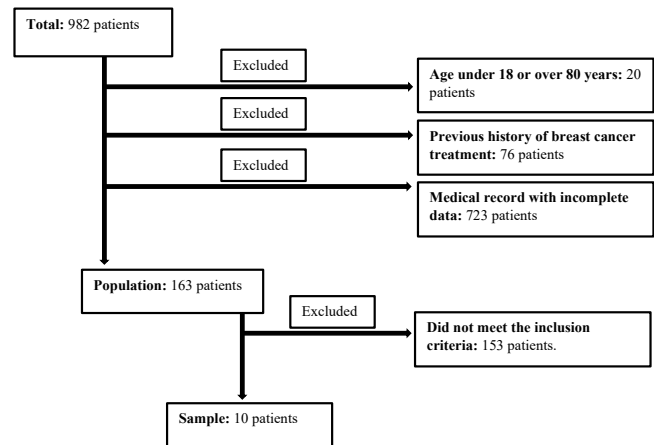


Figure 1. Flow chart of patient selection.

Table 1. Baseline data.

Variables (total of 10 patients)	n (%)
Median patient age: 52 years (34–70)	
Family history*	2 (20)
Axillary involvement on US before neoadjuvant chemotherapy	9 (90)
Clinical axillary involvement	8 (80)
Type of surgery performed	
Segmental resection	7 (70)
Mastectomy	3 (30)
Tumor size (cm)	
1.3–2.0	4 (40)
2.1–3.0	2 (20)
3.1–3.7	2 (20)
Clinical staging	
IIA	6 (60)
IIB	3 (30)
IIIA	1 (10)
Histologic subtype	
Invasive carcinoma of no special subtype	10 (100)
Molecular subtype	
Luminal B	8 (80)
Triple negative	2 (20)
SLN involved	
1/1	2 (20)
1/2	5 (50)
1/3	2 (20)
1/5	1 (10)
Adjuvant systemic treatment	8 (80)
Adjuvant radiotherapy	10 (100)
Local recurrence	1 (10)
Axillary recurrence	0 (0)
Metastasis	3 (30)

*Patients whose first-degree relatives had breast cancer; US: ultrasound; SLN: sentinel lymph nodes.

this patient was luminal B. Two patients (20%) were alive with the disease: one with a triple-negative tumor had lung metastasis and the other with luminal B tumor had bone metastasis. Seven patients were alive and without disease. None of the patients had axillary recurrence. Table 2 indicates patient status after a median follow-up of 37 months.

DISCUSSION

In the current study, with a median follow-up of 39.5 months, there was no axillary recurrence and 90% of the patients were alive. There were three cases of tumor recurrence and one also had a local cancer recurrence. Distant metastases occurred in all patients.

A survey of 310 breast cancer specialists in Europe indicated that 57.3% still performed routine ALND in patients with clinical lymph node involvement who received neoadjuvant chemotherapy, showing that the management of these patients remains controversial¹⁰.

A retrospective study including 161 cases compared outcomes in patients with positive SLN after neoadjuvant chemotherapy who underwent ALND (or not). With a three-year follow-up, the regional control rate was 95.1% for patients undergoing SLN investigation and 95.5% for ALND. In addition, there was a significantly higher incidence of lymphedema in patients undergoing ALND (25.0%) than in the SLN group (9.4%), without a difference in overall survival¹¹.

In another study with a 6-year follow-up, patients underwent SLN investigation, followed by ALND after receiving neoadjuvant chemotherapy. The FN rate was only 8% in the case of SLN-positive and ALND-positive patients at the time of axillary clearance¹².

In our study, a patient undergoing mastectomy and SLN investigation had micrometastasis in an SLN leading to bone metastasis about 12 months after surgery, although she had no axillary disease. On immunohistochemistry, eight patients had estrogen receptor (ER)-positive tumors. Of these, only one underwent a

mastectomy. Of the patients undergoing breast-conserving treatment, all received adjuvant radiotherapy. Two cases developed distant metastasis and one had concomitant breast recurrence.

Some risk factors related to increased FN rate included the administration of neoadjuvant chemotherapy and the investigation of metastasis in only one SLN^{6,13}. To reduce the FN rate, it was shown that technetium combined with dyes, such as patent blue, could increase SLN identification^{6,14}. Furthermore, a study demonstrated that triple-negative (TN), human epidermal growth factor receptor-type 2 (HER-2) positive tumors, with pathologic complete response of the breast on magnetic resonance imaging, were strong predictors of negative SLN¹⁵.

In the current study, all patients underwent SLN investigation with dual tracers. The SLN were identified in all cases and a mean number of two SLN were removed. Only two patients (20%) had a TN tumor; both had positive SLN in the nodes removed. None of our cases was HER-2 positive and magnetic resonance imaging was not performed for the evaluation of clinical response.

A study demonstrated that there was no correlation between the size of SLN metastasis and the rate of positive non-SLN in patients undergoing ALND with positive SLN after neoadjuvant chemotherapy. This corroborates the administration of adjuvant radiotherapy treatment to all positive SLN patients undergoing neoadjuvant chemotherapy. We should be aware that no one can be certain about axillary node involvement, other than the SLN¹¹. Furthermore, another study reported a significant relationship between adjuvant radiotherapy and survival in patients with positive SLN following chemotherapy, who had not undergone ALND¹⁶. In contrast, a paper showed patients with clinical evidence of axillary lymph node involvement who underwent ALND only and did not receive adjuvant or neoadjuvant systemic treatment. It was comprised of 101 patients with ER-positive and HER-2 negative tumors. This paper reported that lymph node metastasis larger than 1 cm, lobular histology, and tumor size larger than 5 cm were associated with residual axillary disease

Table 2. Patient status according to characteristics of the recurrence after a median follow-up of 37 months.

Case	Histologic subtype	Status	Recurrence site
01	Luminal B	Alive without disease	-
02	Luminal B	Death from disease	Breast, lungs, liver, and central nervous system
03	Luminal B	Alive with disease	Bones
04	Luminal B	Alive without disease	-
05	Luminal B	Alive without disease	-
06	Luminal B	Alive without disease	-
07	Luminal B	Alive without disease	-
08	Triple-negative	Alive with disease	Lungs
09	Luminal B	Alive without disease	-
10	Triple-negative	Alive without disease	-

at a later stage. In 40% of patients, there was minimal axillary disease and ALND could be omitted¹⁷.

In our study, all patients had clinically positive axilla. Only two (20%) did not receive adjuvant systemic treatment, both had HER-2 negative breast cancer, and one also had ER-positive tumor. The patient who had HER-2 negative and ER-positive cancer died due to disease progression with local recurrence and distant metastasis. However, the patient who was only HER-2 negative had no evidence of active disease at 46 months.

A prospective study assessed the role of positron emission tomography (PET)-computed tomography (CT) scan in the evaluation of response in clinically positive axilla before neoadjuvant chemotherapy. Following the completion of neoadjuvant chemotherapy, when no suspicious axillary lymph nodes were detected on PET-CT scan and the SLN was negative, none of the patients had nodal involvement in other lymph nodes after ALND. The authors pondered that ALND could be omitted in this scenario¹². In our study, routine PET-CT scan for patient evaluation was not carried out, due to the high cost of the imaging test. It was used only when distant metastases were suspected.

In a study conducted in 2021, Chun et al. described that morbidity caused by ALND could be prevented without reducing cancer control in patients with a limited burden of nodal disease after neoadjuvant chemotherapy. In that retrospective study, 324 patients were included and the 5-year axillary disease-free survival and overall survival rates in patients undergoing SLN investigation only were 91.6% and 93.6%, respectively¹⁶.

Our study had limitations inherent to retrospective studies besides the small number of cases (only 10). It did not enable us to draw conclusions about oncologic outcomes or modify patient management from the literature. Nevertheless, our case study encompassed an emerging theme in breast disease. In the next five years, it is possible that a randomized clinical trial on this subject is yet to be published. As a result, many women will still undergo ALND and suffer considerable morbidity.

Multicenter retrospective cohort studies should be conducted to confirm or not these initial results since many surgeons have adopted this approach despite the small number of publications on the topic. ALND is omitted following neoadjuvant chemotherapy in patients with positive SLN. This should occur after the patient is informed about the risks and benefits involved, preferably in tumor board sessions. Dual tracers for SLN identification are essential. Clipping of suspicious lymph nodes seems to have a significant role that is still not fully defined. Furthermore, it increases treatment costs. Axillary exploration during surgery is fundamental to avoid leaving residual macroscopic disease which may represent resistant clones to neoadjuvant chemotherapy and worsen patient survival.

CONCLUSIONS

In the current study, none of the patients exhibited axillary recurrence in a median follow-up of 39.5 months after ALND was omitted in the presence of positive SLN following neoadjuvant chemotherapy.

AUTHORS' CONTRIBUTION

LMFC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. MSCL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. REARC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. TPD: Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. SCV: Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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