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ORIGINAL RESEARCH

Arm lymphoscintigraphy after axillary lymph node dissection or sentinel lymph node biopsy in breast cancer

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Purpose: Compare the lymphatic flow in the arm after breast cancer surgery and axillary lymph node dissection (ALND) versus sentinel lymph node biopsy (SLNB) using lymphoscintigraphy (LS).

Patients and methods: A cross-sectional study with 39 women >18 years who underwent surgical treatment for unilateral breast cancer and manipulation of the axillary lymph node chain through either ALND or SLNB, with subsequent comparison of the lymphatic flow of the arm by LS. The variables analyzed were the area reached by the lymphatic flow in the upper limb and the sites and number of lymph nodes identified in the ALND or SLNB groups visualized in the three phases of LS acquisition (immediate dynamic and static images, delayed scan images). For all analyses, the level of significance was set at 5%.

Results: There was a significant difference between the ALND and SLNB groups, with predominant visualization of lymphatic flow and/or lymph nodes in the arm and axilla (P=0.01) and extra-axillary lymph nodes (P<0.01) in the ALND group. There was no significant difference in the total number of lymph nodes identified between the two groups. However, there was a significant difference in the distribution of lymph nodes in these groups. The cubital lymph node was more often visualized in the immediate dynamic images in the ALND group (P=0.004), while the axillary lymph nodes were more often identified in the delayed scan images of the SLNB group (P<0.01). The deltopectoral lymph node was only identified in the ALND group, but with no significant difference.

Conclusion: The lymphatic flow from the axilla was redirected to alternative extra-axillary routes in the ALND group.

Keywords: breast neoplasms, lymphadenectomy, radionuclide imaging, lymphatic diseases

Introduction

Breast cancer treatment has evolved over recent decades due to advances in techniques for early detection of the disease, with consequent decreases in the mortality rate[1,2] and morbidity rate that result from less aggressive surgeries. The status of axillary lymph nodes determines whether the treatment should be more or less invasive, indicating either axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB),[3–5] respectively. Surgical injuries resulting from ALND cause obstruction of the primary route of lymphatic drainage of the arm,[5,6] leading to postoperative complications, such as hemorrhage, infection, seroma, axillary web syndrome, chronic pain, paraesthesia caused by intercostobrachial nerve damage, reduced range of motion and muscle weakness on the shoulder ipsilateral to the surgery, and, especially, lymphedema.[7,8] More conservative intraoperative techniques to approach the axillary chain, such as SLNB have been used

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in an attempt to prevent lymphedema. Krag et al[9] and Giuliano et al[10] introduced innovative techniques that represent a new standard of axillary treatment for patients in the early stages of breast cancer, allowing a selective, safe, and less mutilating resection with satisfactory results and a significant reduction of surgical morbidities.[11,12] However, this treatment is limited to patients with clinically negative axilla.[13,14] The main goal of SLNB is to provide information about the stage and prognosis of the axillary chain to avoid unnecessary axillary lymphadenectomy, consequently decreasing morbidities in the upper limb ipsilateral to the axilla manipulated. Although this surgical technique has been improved, its use reduces but does not eliminate the risk of developing lymphedema,[15,16] which has an incidence of 0%–13%.[6,17,18] Several factors can lead to this condition, such as the transection of lymphatic vessels of the arm during the SLNB[19,20] and obesity.[20,21] The increased incidence of lymphedema, especially associated with complementary radiotherapy,[22,23] impacts the quality of life of these patients.[24]

Once established, lymphedema is incurable. Studies have demonstrated that both surgical and drug therapies have failed in the cure of the disease.[25] However, lymphedema can be avoided, treated, and controlled through daily preventive measures.[26] Its diagnosis is difficult, especially in the early stages.[23] Without a correct early diagnosis, the treatment begins late and at more advanced stages of the disease. Immediate treatment leads to rapid improvement and prevents disease progression.[27] The lymphatic system is anatomically complex and difficult to image. For a long time, lymphatic imaging was limited to the use of conventional lymphography, which is an invasive procedure with a high incidence of discomfort and complications.[28]

Lymphoscintigraphy (LS) has been used since 1950 to study diseases associated with the lymphatic system. Initially, it was used qualitatively to determine the relationship between edema of the extremities and lymphatic system disorders without any association with etiology. In the past three decades, the use of quantitative analysis was implemented.[29,30] Numerous studies have demonstrated the reliability of the lymphatic flow studies, regardless of modes of investigation, radiotracers, and interpretation, as described by Akita et al[31] using indocyanine green fluorescence imaging for lower leg lymphedema investigation following lymph node dissection for gynecologic cancer.

In mastology, LS is widely used for SLNB. There are no data in the literature on the use of LS to evaluate the lymphatic drainage pathway of the upper limb after SLNB.

In agreement with the new guidelines for the use of more conservative surgical procedures, this study aimed to analyze changes in the lymphatic flow of the arm by LS after ALND versus SLNB performed for postoperative breast cancer.

Patients and methods

This prospective cross-sectional study selected 39 women $>$18 years who underwent surgical treatment for unilateral breast cancer and either ALND or SLNB as the axillary lymph node chain approach between 2005 and 2012. The lymphatic flow of the arm in the postoperative period was compared between the two lymphatic manipulation techniques. LS was performed up to 60 days after the surgery. An arm range of motion corresponding to $>$120° of shoulder flexion was also required for women who underwent ALND. The exclusion criteria were as follows: patients who underwent chemotherapy or radiotherapy before surgery, patients with knowledge of the lymphatic pathology before ALND and SLNB, and presence of inflammatory or infectious processes associated with arms. The Research Ethics Committee of Barretos Cancer Hospital approved this study, and all patients signed an informed consent form.

All lymphoscintigraphies were performed with a standardized acquisition technique according to the protocol developed by Sarri et al[29] using a dual-head gamma camera (GE Medical Systems Israel Ltd, Millennium VG Hawkeye, Tirat Hacarmel, Israel) equipped with a low-energy high-resolution collimator with a 20% window centered around the 140 keV photopeak and matrices of 128×128 for dynamic images, 256×256 for static images, and 256×1,024 for the whole-body scan (WBS), with no magnification. With patients in the supine position and arms raised above the head, 37 MBq of 99m Tc-phytate (Nuclear and Energetic Research Institute – IPEN, FITA-TEC fitato de sódio [99m Tc], São Paulo, Brazil) by volume of 0.5 mL was administered subcutaneously (fan technique) into the second interdigital space[29] of the manipulated limb using an insulin syringe. Dynamic images were obtained immediately after injection at a rate of 1 minute per image for 20 minutes for a field of view including the area from the hands to the axillae (Dynamic). Two static images with time of 500 seconds were acquired immediately after the end of the Dynamic: one was acquired in the same field of view as the Dynamic projection (Static 1), and the other was acquired in the anterior thoracic region and axillae projection (Static 2). With the patient in the same position, a WBS at a bed speed of 7 cm/minute started 90 minutes after injection of the radiotracer and included anterior and posterior projections. The patients attended the LS procedures wearing appropriate clothing that would not restrict the superficial lymphatic flow.

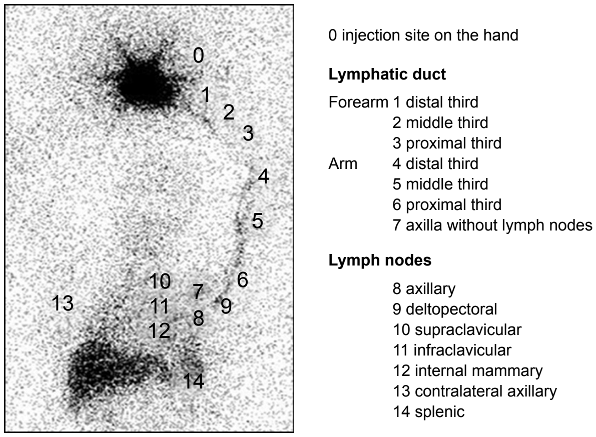

Figure 1 Lymphoscintigraphy including the area from the hand to the abdominal region.
Notes: Sequential ordinal classification of the site reached by lymphatic flow from the injection site (minimum classification) to the spleen (maximum classification).
Source: Reprinted with permission from Sarri AJ, Moriguchi SM, Dias R, et al. Physiotherapeutic stimulation: Early prevention of lymphedema following axillary lymph node dissection for breast cancer treatment. *Exp Ther Med*. 2010;1(1): 147–152.[29]

Qualitative analysis

The lymphoscintigraphies from the two groups were analyzed based on the area reached by the radiotracer in the lymphatic ducts of the upper limb and on the sites and number of lymph nodes visualized in the three phases of LS acquisition. A sequential ordinal classification was used for the area reached by the lymphatic fluid, from the injection site to the most distant point reached, using a 0–14 scale, respectively, with the number of lymph nodes visualized, as proposed by Sarri et al[29] and is shown in Figure 1.

For statistical analysis, the points reached by the lymphatic fluid were grouped into the forearm (points 0–3), arm and axilla (points 4–9), and extra-axillary lymph nodes in the thoracic region (points 10–12). The images acquired in the three phases of the LS of women who underwent ALND and SLNB were paired and compared. Frequencies, percentages, and measures of central tendency and dispersion were used to characterize the sample. The Mann–Whitney *U* test was used to compare the number of lymph nodes visualized, age, and body mass index (BMI) between the ALND and SLNB groups (Table 1) and descriptive analysis in Table 2. Fisher's exact test was used to compare the qualitative variables (Table 3). For all analyses, the level of significance was set at 5%.

Results

The sample analyzed (n=39) consisted of two groups of patients: patients who underwent ALND (n=22) and patients who underwent SLNB (n=17). The mean age and BMI were similar between the groups, but there was a significant difference in the number of lymph nodes removed ($P<0.01$) and in the number of positive lymph nodes, evident only in the ALND samples, as shown in Table 1. The patients with positive sentinel lymph nodes were sequentially submitted to ALND and excluded from the study.

A total of 54.5% (n=12) of patients who underwent ALND and 35.3% (n=6) of patients who underwent SLNB had surgery on the right breast. Regarding the type of surgery, conservative and partial surgeries were predominant in the SLNB group, while in the ALND group, ~50% of the patients underwent radical mastectomies, as shown in Table 2. Only 23.5% (n=4) underwent immediate breast reconstruction, and these patients were from the SLNB group.

The lymph ducts were more evident in the early LS images, which were acquired within up to 40 minutes (Dynamic and Static 1, 2), with the arm and axilla being the most frequent sites reached by the lymphatic fluid in both groups analyzed (ALND × SLNB), with no significant difference. The delayed LS images at 90 minutes (WBS) identified significant differences between the ALND and SLNB groups, with predominant visualization of lymphatic flow and/or lymph nodes in the arm and axilla in the ALND group ($P=0.01$) (Figure 2) and of extra-axillary lymph nodes only in the ALND group ($P<0.01$), as shown in Table 3.

There was no significant difference in the total number of lymph nodes identified between the ALND and SLNB groups. However, there was a significant difference in the distribution of lymph nodes in these groups. The cubital lymph node was more frequently visualized in the immediate

Table 1 Descriptive statistics of the sample ALND and SLNB groups

Variable	ALND			SLNB			*P*-value (M–W)
	n	Mean (SD)	Min–max	n	Mean (SD)	Min–max	
Age (years)	22	51.0 (0.0)	26.0–71.0	17	53.9 (9.0)	36.0–73.0	0.27
BMI (kg/m^2)	22	27.4 (5.2)	18.0–40.7	17	26.9 (4.0)	19.3–34.4	0.96
RLN (number)	22	19.0 (6.2)	11.0–34.0	17	1.6 (0.8)	1.0–3.0	<0.01
PLN (number)	22	4.3 (6.2)	0.0–22.0	17	0.0 (0.0)	–	–

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; M–W, Mann–Whitney *U* test; PLN, positive lymph nodes; RLN, removed lymph nodes; SD, standard deviation; SLNB, sentinel lymph node biopsy.

Table 2 Types of surgery in ALND and SLNB groups

Type of surgery	ALND, n (%)	SLNB, n (%)
Patey's mastectomy	6 (27.3)	0 (0.0)
Madden's mastectomy	4 (18.2)	0 (0.0)
Simple mastectomy	2 (9.1)	2 (11.8)
Skin-sparing mastectomy	0 (0.0)	1 (5.9)
Quadrantectomy	10 (45.5)	14 (82.4)
Total	22 (100)	17 (100)

Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Dynamic imaging in the ALND group (P=0.004), while the axillary lymph nodes were more frequently visualized in the delayed imaging (WBS) in the SLNB group ($P<0.01$) (Figure 3). The deltopectoral lymph node was identified only in the ALND group (Figure 4), but without a significant difference, as shown in Table 4.

Table 3 Sites reached by the lymphatic flow in the ALND and SLNB groups distributed over the dynamic, static, and WBS image stages and classified into forearm, arm/axilla, and thoracic extra-axillary lymph nodes

Progression	Group		*P*-value[a]
	ALND, n (%)	SLNB, n (%)	
Dynamic images			
Forearm	6/18 (33.3)	5.16 (31.2)	0.99
Arm/axilla	12/18 (67.7)	11/16 (68.8)	0.99
Thoracic LN	0/18 (0.0)	0/16 (0.0)	–
Static images			
Forearm	3/19 (15.8)	3/16 (18.7)	0.99
Arm/axilla	16/19 (84.2)	13/16 (81.3)	0.65
Thoracic LN	0/19 (0.0)	0/16 (0.0)	–
Whole-body scan			
Forearm	0/19 (0.0)	0/16 (0.0)	–
Arm/axilla	11/19 (57.9)	2/16 (12.5)	0.01
Thoracic LN	8/19 (42.1)	0/16 (0.0)	<0.01

Note: [a]Fisher's exact test.
Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; LN, lymph nodes; WBS, whole-body scan.

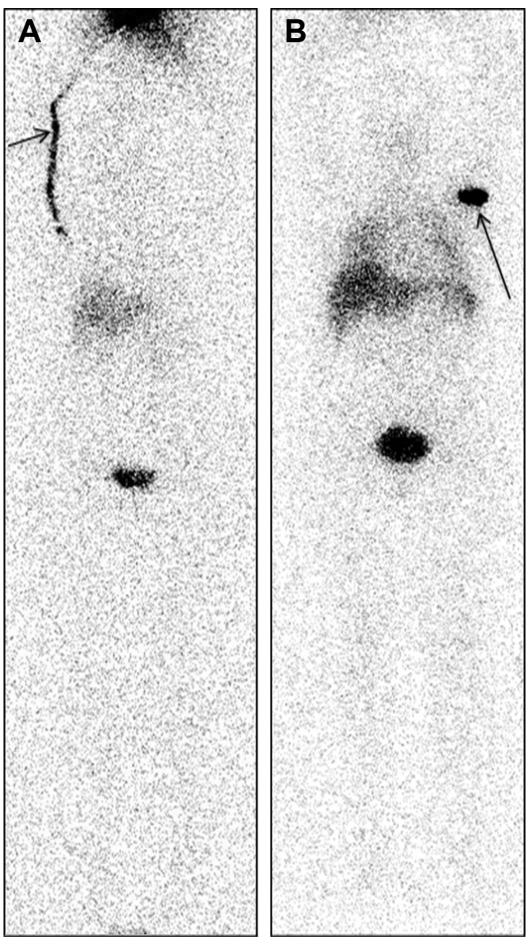

Figure 2 Difference in lymphatic progression between the (**A**) ALND and (**B**) SLNB groups. WBS of the ALND and SLNB groups.
Notes: (**A**) Arrow points to the persistent visualization of lymphatic ducts in the upper limb with no evidence of lymph nodes (lymphatic stasis). (**B**) Arrow points to the usual visualization of axillary lymph nodes.
Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; WBS, whole-body scan.

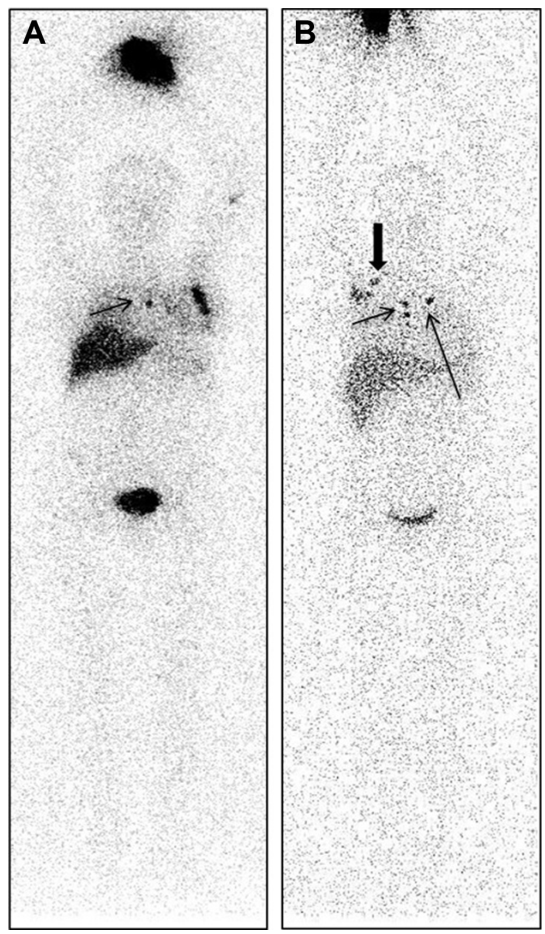

Figure 3 WBS of the ALND group.
Notes: Extra-axillary lymph nodes in addition to axillary lymph nodes. (**A**) Internal mammary lymph nodes on the left (short arrow). (**B**) Infraclavicular lymph node on the right (thick arrow), internal mammary chain lymph nodes on the left (long arrow), internal mammary chain lymph nodes on the right (short arrow).
Abbreviations: ALND, axillary lymph node dissection; WBS, whole-body scan.

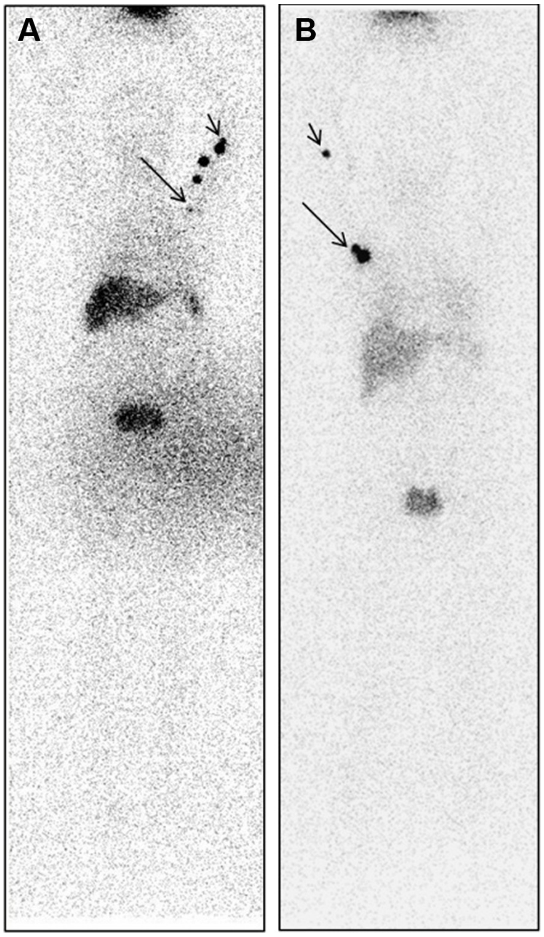

Figure 4 Lymphoscintigraphy. Different distributions of lymph nodes in the ALND and SLNB groups.

Notes: (**A**) ALND group – Cubital lymph nodes (short arrow) slightly visible in the axillary region (long arrow). Deltopectoral lymph nodes between the two arrows. (**B**) SLNB group – Lymph nodes identified in the cubital region (short arrow) and well visualized in the axillary region (long arrow).

Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; WBS, whole-body scan.

Table 4 Location of lymph nodes in the ALND and SLNB groups observed in the dynamic, static, and WBS imaging

Progression	Group		*P*-value[a]
	ALND, n (%)	SLNB, n (%)	
Cubital lymph node			
DI	5/19 (26.3)	0/16 (0.0)	0.004
SI	4/20 (20.0)	5/16 (31.2)	0.470
WBS	8/19 (42.1)	7/12 (58.3)	0.473
Deltopectoral lymph node			
DI	2/19 (10.5)	0/16 (0.0)	0.489
SI	3/20 (15.0)	0/16 (0.0)	0.238
WBS	3/19 (15.8)	0/12 (0.0)	0.265
Axillary lymph node			
DI	2/19 (10.5)	4/16 (25.0)	0.379
SI	3/20 (15.0)	5/16 (31.2)	0.422
WBS	7/19 (36.8)	12 (100.0)	<0.01

Note: [a]Fisher's exact test.

Abbreviations: ALND, axillary lymph node dissection; DI, dynamic imaging; SLNB, sentinel lymph node biopsy; SI, static imaging; WBS, whole-body scan.

Discussion

Currently, the implementation of modern surgical techniques for patients with breast cancer seeks to minimize the risk of treatment-associated morbidities, particularly lymphedema,[8,32,33] with a subsequent decline in ALND practice after positive SLNB for micrometastases or isolated tumor cells, suggesting that ALND is more prognostic than therapeutic.[34]

Lymphedema develops when the rate of production of lymphatic fluid exceeds the capacity of lymph transport. It is characterized by lymphatic fluid accumulation in the interstitial space (edema), which often occurs in the extremities.[35,36] Once established, lymphedema is incurable, and it is difficult to diagnose, especially in the early stages.[12] Without a correct diagnosis, treatment begins late and at a more advanced stage of the disease. Immediate treatment leads to rapid improvement and also prevents the progression of the disease to the chronic phase.[16,23] The concern of patients regarding lymphedema development was reported by McLaughlin et al[34] who found that 50% of patients who underwent SLNB versus 75% of patients who underwent ALND were concerned about the development of this disease. Despite reports showing that the concerns of patients who underwent SLNB are unfounded due to the low risk of developing lymphedema, preventive measures should be taken because, although low, the risk exists. Several factors are attributed to the development of lymphedema after the SLNB and ALND procedures, such as the rupture of lymphatic vessels of the arm;[19,20,37] the fact that the sentinel lymph node draining to the breast and upper limb is the same and that its removal disrupts lymphatic drainage;[38] obesity;[20,21] poor surgical techniques;[39] low educational level; advanced stage of disease; infections; number of lymph nodes involved; associated comorbidities; trauma; time after surgery;[36] anatomical peculiarities of the lymphatic system, which vary among patients;[35] and combination with adjuvant radiotherapy.[40,41]

Nuclear medicine technology plays an important role in evaluating the pattern of lymphatic drainage.[42,43] The lymphatic system is complex, and its imaging remains a challenge. First, the lymphatic system is not an organ but connects different structures of small lymphatic capillaries to main ducts through lymph nodes and valves. Each of these structures can be visualized separately in images. Second, the lymphatic system can comprise a variety of diseases, including neoplasias and infectious diseases.[16,18,44] Studies using LS to evaluate the lymphatic circulation of the arm immediately after surgical treatment in patients with breast cancer (ALND and SLNB) were not found in the literature, so comparisons with this study could not be performed. This study was able to evaluate the lymphatic route in the early and delayed phases of scintigraphy in both groups. The delayed LS images (WBS) were more significant in identifying the differences in the lymphatic alterations between the ALND and SLNB groups. It is possible that a larger sample might generate a significant difference.

Using LS, Celebioglu et al[35] qualitatively and quantitatively compared the operated and nonoperated upper limbs of patients who underwent ALND and SLNB, where the second examination was 2–3 years after surgery and radiotherapy. The authors found a difference in the ALND group, where patients had dermal backflow and decreased accumulation of radiotracer in the axilla, while there was no difference in the SLNB group. In this study, dermal backflow was not visualized in any patient, most likely due to the short interval between the surgery and the LS. An attempt to maintain the lymphatic flow through alternative routes was identified. Additionally, more axillary lymph nodes were observed in the SLNB group, obviously due to the preservation of the axilla in this group. In contrast, a greater number of extra-axillary lymph nodes, especially in the cubital and deltoid regions, were observed in the ALND group. This finding is most likely due to damage to the normal lymphatic circulation, with flow redirected to alternative routes of deeper lymphatic chains, confirming the study conducted by Sarri et al[29] comparing lymphatic drainage before and after ALND. These findings show an attempt to maintain the lymphatic flow of the upper limb after more aggressive surgeries. Lymphoscintigraphies performed at longer intervals after surgery (a minimum of 6 months after) may clarify the impact of these findings. Further studies should be conducted at such intervals to try to better elucidate these points.

Conclusion

In conclusion, the data from this study showed lymphatic damage, with the lymphatic flow from the axilla being redirected to alternative routes in the ALND group in early postoperative breast surgery.

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Disclosure

The authors report no conflicts of interest in this work.

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