Preoperative upper limb lymphatic function in breast cancer surgery

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Summary

Objective: To describe the preoperative upper limb lymphoscintigraphic pattern in women with breast cancer. **Methods:** Thirty-seven patients undergoing lymphoscintigraphy within 30 days of surgery were investigated. Lymphoscintigraphic studies of 37 upper limbs ipsilateral to surgery and 32 contralateral upper limbs were performed. The examination protocol consisted in obtaining static images of the upper limb in semi-flexion after 10 minutes, and 1 and 2 hours after subcutaneous injection of 1 mCi (37 MBq) of Tc-99m-dextran in the dorsum of the hand. The velocity of axillary lymph node visualization (I, visible at 10 minutes; II, 1 hour; III, 2 hours; and IV, invisible) and degree (intensity) of nodal uptake (a, marked; b, moderate; c,mild; and d, absent) were analyzed. **Results:** Optimal lymphatic functional pattern (Ia) was observed in four (11%) patients, in the ipsilateral upper limb, and six (19%), in the contralateral upper limb. Worse condition was observed in three (8%) patients (IVd) in the ipsilateral upper limb and two (6%) patients in the contralateral upper limb. The remaining patients showed intermediate states of velocity and uptake intensity. **Conclusion:** This study found relevant changes in preoperative lymphoscintigraphy, demonstrating preexisting functional differences in the lymphatic system.

Keywords: Lymphatic system; lymphedema; breast neoplasm; radionuclide imaging; lymph node excision; lymphangiogenesis.

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Introduction

The lymphatic system is a component of the human body closely related to the venous system and of which we have limited scientific knowledge[1]. It has important functions and, among them, are control of macromolecular homeostasis, absorption of lipids, immunologic function, and control of tissue fluids[2]. Its main function is the removal of lipids and proteins from interstitial spaces. Removal of those elements, on the other hand, is possible through the capillary lymphatic membrane, which is more permeable than the epithelial membrane of blood vessels. Thus, when failure of the lymphatic system occurs, the development of lymphedema is observed[3].

The etiology and risk factors for the development of lymphedema in postoperative breast cancer patients seem multifactorial and are not fully understood. The risk of developing lymphedema is associated with axillary dissection, axillary radiotherapy, obesity, extension of the surgical technique, infection[4], age, number of lymph nodes dissected, number of affected lymph nodes, and level of lymph node removal[5]. However, these associations were not maintained in other studies[6-8].

Little is known on the preoperative anatomic and functional characteristics of the lymphatic system, and, therefore, we consider that all patients have normal upper limb lymphatic function. However, the similar prevalence of postoperative lymphedema after breast cancer surgery among patients with unilateral and bilateral axillary dissection does not corroborate this hypothesis[9].

Lymphoscintigraphy is currently proposed as the main diagnostic test to investigate the peripheral lymphatic system, allowing visualization of lymphatic vessels and lymph nodes, as well as the quantification of lymphatic transport, being used in clinical practice to indicate and quantify the function of the lymphatic system, on the morphologic and functional point of view, determine the number of sentinel lymph nodes, and identify patients at risk for the development of lymphedema after lymph node dissection[10].

Currently, it is difficult to establish the ideal classification for the functional status of the upper limb lymphatic system, since those scales are created empirically[11]. Some authors have proposed an assessment of lymphatic transport through dynamic lymphoscintigraphy by analyzing the time of appearance of the radiopharmaceutical on the lymph node[12], according to the quality of the image[13], and by static lymphoscintigraphy to visualize axillary lymph nodes[11,14]. The majority of studies established 10 minutes as the normal time for transportation of the radiopharmaceutical, considering 1 hour delayed transport, and two hours as seriously compromised transport[15-17].

It is believed that prior assessment of the upper limb ipsilateral to the surgery allows the detection of anatomical and functional abnormalities of lymphatic distribution, enabling more accurate analysis of postoperative changes in the ipsilateral upper limb[18]. Early evidence of those changes would allow the development of preventive actions, stricter follow-up, and, possibly, perform early diagnosis and treatment. Thus, the objective of the present study was to describe the preoperative lymphoscintilographic pattern of the upper limb in females with breast cancer before mastectomy with axillary dissection.

Methods

This is a descriptive study that evaluated 37 women in the preoperative period of unilateral mastectomy with lymph node dissection in the three Berg levels for invasive breast carcinoma. Thirty-seven lymphoscintigraphies of the upper ipsilateral limb and 32 of the contralateral limb were performed. Patients with prior breast and axillary surgery, infection of the upper limb, lymphedema – diagnosed by a 2-cm difference in circumference of the upper limbs, were excluded. Other exclusion criteria were: bilateral surgery, indication of sentinel lymph node biopsy prior to axillary dissection, and preoperative radiotherapy.

The idea and realization of this study were based on the Helsinki Declaration[19]. This study was approved by the Ethics on Research Committee of Faculdade de Ciências Médicas of Universidade Estadual de Campinas (UNICAMP) and all patients signed and informed consent, but two of them refuse to participate in the study.

Lymphoscintigraphic technique

The lymphoscintigraphic protocol is not standardized and differs according to the diagnostic center performing it. Differences include the choice of the radiopharmaceutical, type, and place of injection, use of static or dynamic evaluations, and intervals to obtain the images[20].

Data pertinent to the lymphatic system were evaluated by lymphoscintigraphy on the Department of Nuclear Medicine of Hospital das Clínicas of UNICAMP, performed preoperatively, no more than 30 days before the surgery. The protocol of the test consisted of static images of the upper limb in semi-flexion obtained with a scintigraphic camera ELSCINT SP4 or ELSCINT SP6, with the patient in dorsal decubitus, 10 minutes, 1 and 2 hours after subcutaneous injection of 1 mCi (37 MBq) of Tc-99m dextran on the dorsum of the hand[20]. The upper limb was maintained at rest in the interval between images. The injection was performed by nurses' aides properly trained.

Lymphoscintigraphic interpretation

Interpretation of the test is better done based on recognition of abnormal distribution of the radiopharmaceutical and knowledge of the relative time that takes the radiopharmaceutical to reach regional lymph nodes[21]. Thus, analysis of intensity of capture of axillary lymph nodes and the speed of their appearance was performed before the surgery.

In the present study, the time it took the radiopharmaceutical to reach axillary lymph nodes[22] was called velocity, and the accumulation (intensity) of the radiopharmaceutical in axillary lymph nodes[10], degree. Gloviczki et al.[16] also used these combined parameters to establish a classification criteria, since the literature does not have a standard criteria established for quantitative evaluation of lymphoscintigraphy.

According to this proposal, the ideal pattern of normalcy considered was Ia, and IVd as total disruption of lymphatic function. The remaining patterns reflect intermediate stages of disruption. Thus, images were evaluated according to Box 1.

Lymphoscintigraphic studies were analyzed by two nuclear experts on different moments and, in case of disagreement, the exam was analyzed by a third nuclear expert. Concordance among evaluators, regarding degree and velocity, was excellent, according to the Kappa coefficient[23].

Results

Thirty-seven patients with invasive breast carcinoma scheduled to undergo radical mastectomy were submitted to ipsilateral upper limb lymphoscintigraphic studies, while 32 underwent contralateral studies. Regarding tumor staging, three patients were EI, fourteen, EII, sixteen, EIII, three, EIV, and in one case, staging was not possible. Twenty-six of them (70%) had clinical axillary involvement. Other clinical characteristics are presented on Table 1.

Among the results of the ipsilateral upper limb, 18 women (49%) had velocity I, 14 (38%), velocity II, 2 (5%), velocity III, and 3 (8%), velocity IV. As for the degree, 8 women (22%) had degree a, 13 (35%), b, 13 (35%), c, and 3 (8%), d.

Among the results of the contralateral upper limb, 14 women (44%) had velocity I, and 14 (44%), II. Two women (6%) had velocity III, and 2 (6%), IV. Regarding the degree, 8 women (25%) had degree a; 13 (41%), b; 9 (28%), c; and 2 (6%), d.

Considering parameters of velocity and degree for a single classification, it was observed that only 4 patients (11%) had classification Ia, considered the normal pattern, on the ipsilateral upper limb versus 6 (19%) patients in the contralateral upper limb. Three (8%) and two (6%) patients were classified IVd, respectively, considered complete disruption. The other patients were classified as follows: 8 (22%) vs. 4 (12.5%), Ib, 6 (16%) vs. 4 (12.5%), Ic, 4 (11%) vs. 2 (6%), IIa, 3 (8%) vs. 7 (22%), IIb, 7 (19%) vs. 5 (16%), IIc, 1 (3%) vs. 0, IIIa, and 1 (3%) vs. 2 (6%), IIIb.

Discussion

The objective of the present study was to describe the preoperative functional pattern of the lymphatic system of the upper limb, through lymphoscintigraphy, in women with breast cancer to analyze intrinsic patient conditions as possible predictive factors to be considered in the development of lymphedema.

The initial difficulty of this study was to establish a reproducible classification for the functional status of the upper limb lymphatic system, since those scales are created empirically[11]. We decided to group the analysis by degree and velocity enabling static evaluation of the degree of capture of the radiopharmaceutical in the axillary lymph nodes and the transportation velocity of this drug through lymphatic vessels on the three moments analyzed, as well as allowing its reproducibility.

Box 1 – Classification of velocity and degree of capture by lymph nodes in lymphoscintigraphy

Velocity		Degree	
I	Lymph nodes visible at 10 minutes	a	Marked capture of the radiopharmaceutical in the lymph nodes
II	Lymph nodes visible after 1 hour	b	Moderate capture of the radiopharmaceutical in the lymph nodes
III	Lymph nodes visible after 2 hours	c	Subtle capture of the radiopharmaceutical in the lymph nodes
IV	Lymph nodes not visible (without visible capture to the human eye)	d	Absence of capture of the radiopharmaceutical in the lymph nodes

Table 1 – Description of some clinical characteristics

	Mean	Standard deviation	Minimum	Maximum	Median
Age (years)	60.1	13.0	34.6	83.7	62.7
Weight (kg)	71.1	15.3	44.0	110.0	70.0
Height (m)	1.6	0.1	1.4	1.8	1.6
BMI (kg/m^2)	28.0	5.2	18.6	41.0	27.5
Number of sessions of QT before the surgery	1.5	2.1	0.0	6.0	0.0

kg, kilogram; m, meter; BMI, body mass index; QT, chemotherapy.

Cambria et al.[12] proposed the evaluation of the lymphatic transportation through dynamic lymphoscintigraphy by analyzing the time of emergence of the radiopharmaceutical in the lymph node. This scale also considered the transportation of the lymphatic movement, distribution of lymphatic pathways, and visualization of lymph nodes and lymphatic vessels. On the other hand, O'Mahony et al.[13] proposed a classification according to the quality of the image, respecting the definition of lymphatic vessels as very poor, poor, adequate, good, and excellent. Szuba et al.[11] developed an empirical scale of static lymphoscintigraphy to visualize the axillary lymph nodes, considering normal pattern visible and symmetrical lymph nodes and, worse pattern as non-visible lymph nodes.

Lymphoscintigraphy is considered normal if discrete lymphatic vessels drain the extremity of the limb and if regional lymph nodes are visualized in up 1 hour[14]. Lane et al.[17] performed lymphoscintigraphic studies every 10 minutes for 1 hour. Weissleder and Weissleder[15] considered normal the appearance of the radiopharmaceutical in the lymph nodes in 10 minutes. Gloviczki et al.[16] also established 10 minutes as the normal time of transportation of the radiopharmaceutical, considering 1 hour delayed transportation and 2 hours seriously compromised transportation.

The intrinsic characteristic of lymphatic drainage is not considered when patients undergo surgery for breast cancer, only postoperative factors are investigated as risk or not. This study demonstrated that the pattern considered ideal (Ia) was observed in only four patients (11%), in the ipsilateral limb, and in 6 patients (19%), in the contralateral limb.

Three patients (8%) had classification IVd, on the ipsilateral limb, and two (6%), on the contralateral limb, considered the worse functional pattern because the radiopharmaceutical is not visible in any of the moments evaluated, demonstrating significant impairment of lymphatic function. Of those, one patient had classification IVd in both upper limbs. Three patients had BMI above 25 kg/m^2, with staging indicating advanced disease; three patients were older than 60 years, and the only young patient had distant metastasis. Those clinical conditions observed agreed with Bourgeois et al.[22] who observed that age above 60 years and more than three lymph nodes involved represent variables that affect independently non-visualization of axillary lymph nodes. Two of those patients underwent neoadjuvant chemotherapy.

In the present study, patients did not undergo radiotherapy, a known risk factor for lymphedema[8,24], in which significant clinical changes can be observed on preoperative lymphoscintigraphy of the ipsilateral limb, indicating it might have been caused by anatomical and functional patient-related or disease-related components as a consequence of advanced locoregional disease.

To evaluate the influence of axillary disease on the changes observed, lymphoscintigraphic studies were performed on the contralateral limb, and relevant functional changes were also observed. Thus, one can suggest that the variability on lymphatic functional status is also present on the upper limb considered normal.

Little is known about preoperative lymphoscintigraphic study. It is believed that anatomical and functional changes present before the surgery would be important in the development of post-axillary dissection lymphedema. A single study reported an incidence of 7.5% of preoperative abnormalities in the lymphatic system, and 85% of those patients developed lymphedema approximately 34 months after surgery[22].

Baulieu et al.[25] evaluated 32 patients with post-operative edema after corrective surgery of tibial fracture with lymphoscintigraphy performed between two and ten days after the surgery, comparing with the healthy limb. Only patients with compromised lymphatic system developed lymphedema over a 3-month period. Therefore, the authors inferred that preexistent functional changes in the lymphatic system justify the early development of lymphedema.

The objective of this study was to evaluate preoperative lymphatic function in the upper limb, and the results observed, with 33 out of 37 patients of the ipsilateral limb with function outside the pattern considered ideal (Ia), and 26 out of 32 in the contralateral limb, suggest that the anantomo-functional characteristics of patients should be evaluated.

Considering the lymphoscintigraphic studies performed, 86% were classified I or II, for velocity in the ipsilateral limb, and 87%, in the contralateral limb. As for the degree, 92% were degree a, b, or c, in the ipsilateral limb, and 97%, in the contralateral limb. These classifications could be considered normal in clinical practice, since they represent small changes in the lymphatic system. But women who were classified III or IV, for velocity, and d, for the degree, should be referred to preventive programs in the immediate postoperative period, or even preoperatively.

Correlating lymphoscintigraphic findings with common complaints of changes in the upper limbs, which might indicate the onset of lymphedema, is important. Those complaints could reveal, subjectively, changes in the lymphatic system, indicating the need of evaluation for early diagnosis of lymphedema and follow-up conduct. Symptoms, such as feeling a heavy weight or hand being squeeze, increased volume, and changes in sensitivity, have been reported by patients with lymphedema and, rarely, by healthy women and, therefore, are useful early indicators of the development of lymphedema[26], before the possibility of clinical diagnosis through limb cirtometry or volumetric measurements.

Only the long-term follow-up of those patients can reveal whether the postoperative changes observed really indicate an increased risk for the development of lymphedema. Thus, patients with changes in preoperative lymphoscintigraphy could be referred to lymphedema prevention programs earlier and with individualized attention; they could undergo weekly lymphatic drainage, receive orientation for auto-massage at home and preventive orientations.

These results suggest the need lymphoscintigraphy studies in the immediate postoperative period to observe how preoperative findings behave after axillary dissection and to the attempt of lymphangiogenesis.

Conclusion

This study observed relevant changes in preoperative lymphoscintigraphy, demonstrating preexisting functional differences in the lymphatic system.

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