

Lymph Drainage Studied by Lymphoscintigraphy in the Arms after Sentinel Node Biopsy Compared with Axillary Lymph Node Dissection Following Conservative Breast Cancer Surgery

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Purpose: To investigate lymphatic drainage as measured by lymphoscintigraphy in the arms of patients undergoing either sentinel lymph node biopsy (SNB) or axillary lymph node dissection (ALND).

Material and Methods: From January 2001 to December 2002, 30 patients with unilateral invasive breast carcinoma underwent breast-conserving surgery with SNB and 30 patients with ALND. All patients received radiotherapy to the breast. Lymphoscintigraphy was performed, and skin circulation, skin temperature, and arm volume were measured 2–3 years after radiotherapy.

Results: None of the 30 patients who underwent SNB showed any clinical manifestation of lymphedema. Of the 30 patients undergoing ALND, six (20%) had clinical lymphedema, with an arm volume that was >10% larger on the operated than on the non-operated side ($P < 0.01$). Scintigraphically, visual analysis revealed lymphatic dysfunction in three patients, manifested as forearm dermal back flow. Two of these patients also had an increased arm volume. Quantitative analysis showed no differences between the groups, apart from a smaller amount of isotope in the axilla in the ALND group. There was no difference in skin circulation or skin temperature.

Conclusion: Our study shows that lymph drainage in the operated arm compared with the non-operated arm was less affected by SNB than by ALND, and that morbidity associated with SNB was lower than with ALND. However, the results do not confirm our hypothesis that lymphoscintigraphy can reveal differences in lymph circulation that are not evident clinically in the form of manifest lymphedema. The most sensitive clinical method of assessing lymph drainage seems to be measurement of arm volume.

Key words: Arm volume; breast cancer; lymphedema; lymphoscintigraphy; sentinel node biopsy

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Lymphoscintigraphy has been used since the 1950s to study diseases in lymphatic systems. The method was first used qualitatively, to determine whether a swelling in an extremity is due to a disorder in the lymphatic system, with altered transportation of lymph fluid, rather than to some other etiology.

During the last three decades, quantitative analysis, scoring systems, and factor analysis of lymphoscintigraphic data have been suggested for greater diagnostic differentiation (25, 27). CAMPISI

et al. (1) applied lymphoscintigraphy in patients with lymphedema secondary to breast cancer treatment, and showed that the method can demonstrate changes in lymphatic drainage before edema becomes clinically evident.

Axillary lymph node dissection (ALND) has long been an integral part of surgical treatment for invasive breast cancer. Axillary lymph node status has been considered to be the most important independent prognostic factor, after primary tumor

status, for recurrence and survival (4, 6). The procedure is fairly simple, but ALND is associated with considerable morbidity, including lymphedema of the arm, and numbness, stiffness, impaired shoulder movement, and pain (9). The number of excised nodes correlates with the severity of discomfort (11). The morbidity associated with ALND has led to a search for new methods for accurate axillary staging with less pronounced postoperative sequelae. In the early 1990s, GUILIANO et al. (5) presented a new concept of axillary lymph node assessment, namely sentinel lymph node biopsy (SNB). This method rests on the notion of MORTON et al. (13) that the sentinel lymph node is the first lymph node to receive lymphatic drainage from a primary breast cancer and also the node that is most likely to contain metastatic cells. Many studies comparing SNB with histological findings in the ALND specimen have shown that SNB is an accurate predictor of axillary status (5, 28). However, the impact of SNB on the incidence of post-surgical lymphatic insufficiency has not been adequately assessed. If the intention is to evaluate the benefit of SNB compared with axillary clearance on the basis of the frequency of lymphedema, a very large number of patients will be needed. Other authors have chosen to study the difference in morbidity in terms of pain from the upper arm and shoulder (29). We have hypothesized that there may be differences in lymphatic drainage that are not clinically evident as arm edema.

The purpose of this study was therefore to study lymphatic drainage measured by lymphoscintigraphy in the arms of patients undergoing either SNB or ALND. Another aim was to study changes in arm volume and the morbidity from the shoulder and arm region.

Material and Methods

From January 2001 to December 2002, 30 patients with unilateral invasive breast carcinoma underwent breast-conserving surgery and SNB. No further axillary dissection was carried out if the SNB showed no metastatic disease in intraoperative frozen sections or in paraffin section histology with hematoxylin and eosin staining and immunohistochemical staining. These patients were compared prospectively with 30 patients in whom conserving surgery for breast carcinoma had been performed in the same period with complete axillary dissection but in whom pathological examination of the axillary specimen had shown that the lymph nodes were free from tumor metastases; in 10 of these

patients, SNB had revealed either one or two metastases.

All patients received radiotherapy to the operated breast alone. Lymphoscintigraphy and skin circulation, skin temperature, and arm volume measurements were performed 2–3 years after the radiotherapy. The patients received written and oral information about the aims and procedure of the study. The study was approved by the regional ethics and radiation protection committees. Clinical and pathological data for the 60 patients are given in Table 1.

Surgery

In all patients, the breast surgery was breast conserving. Sentinel lymph nodes were identified by using a combined technique with a radiolabeled isotope (usually 40–60 MBq of ^{99m}Tc -nanocolloid; GE Healthcare, Uppsala, Sweden) and vital blue dye (1–2 ml of Patent Blue V; Guerbet, Paris, France). The isotope was injected 4–36 hours prior to surgery, and in most cases a lymphoscintigraphy was performed. The vital blue dye was injected immediately before the operation. Axillary dissection was carried out at levels I and II, i.e., below the axillary vein, without skeletonizing the vein, and beneath the minor pectoral muscle. The long thoracic nerve and the thoracodorsal nerve and

Table 1. Clinical and pathological characteristics of the patients

	ALND (n=30)	SNB (n=30)
<i>Age, years</i>		
Median	56.5	57.5
Range	42–73	40–73
<i>Tumor size, mm</i>		
Median	12	15
Range	6–30	7–26
<i>Tumor type</i>		
Invasive ductal	28	22
Tubulolobular	—	2
Tubular	—	2
Mucinous	—	1
Comedo	1	1
Lobular	1	1
DCIS	—	1
<i>Elston grade</i>		
1	8	10
2	19	14
3	3	5
<i>Receptor status pos</i>		
Estrogen	25	26
Progesterone	25	24
<i>Number of axillary lymph nodes removed</i>		
Median	10	2
Range	5–18	1–5

vessels were preserved, and the intercostobrachial nerve was preserved whenever possible. After axillary dissection, the axilla was drained and, when the amount of daily drainage was $<50\text{ cm}^3$, the drain was removed. The axilla was not drained in the patients who underwent SNB.

Experimental set-up

After arrival, the patients sat in the study room for 20 min before any measurements were performed. All measurements were made with the patient in the supine position.

Room temperature (see below), skin temperature (see below), and skin circulation were measured in that order in an area over the middle of the upper arm. All three measurements were performed by the same examiner. Thereafter, $^{99\text{m}}\text{Tc}$ -nanocolloid was injected in both hands (see below). All measurements were repeated 180 min later.

Arm volume

Arm volumes were recorded in each patient before and 1, 2, and 3 years after the operation, using the water-displacement technique. The displaced water was recorded in milliliters. The volume of both arms was measured at each visit, and the difference between them was designated the possible edema volume. All measurements were made by the same study nurse. Lymphedema was defined as an increase in volume $>10\%$ between the operated and non-operated arm.

Lymphoscintigraphy

All patients were given four subcutaneous injections of 10 MBq $^{99\text{m}}\text{Tc}$ -nanocolloid (colloid particles $<80\text{ nm}$; GE Healthcare, Uppsala, Sweden) in 1 ml of sterile saline. Injections were done in both the first and the second interdigital space of each hand. Imaging was performed on a twin-head gamma camera (E-CAM; Siemens, Erlangen, Germany) equipped with LEHR collimators. The activity in the syringes was measured before and after injection, on the same gamma camera. The patients were scanned in the supine position with the arms alongside the body. The scanning speed was 15 cm/min, with a scan length of 80 cm. Imaging was performed immediately after and 30 min, 45 min, 1 hour, 2 hours, and 3 hours after the injection.

Post-processing was carried out on a Hermes workstation (Nuclear Diagnostics, Stockholm, Sweden). Visual and quantitative evaluations were performed. Criteria for lymphatic dysfunction at

visual evaluation were: asymmetrical or absent visualization of lymphatic channels, collateral lymphatic channels, absent tracer uptake in axillary lymph nodes at 3-hour imaging, and presence of dermal back flow. For quantitative analysis, symmetrical regions of interest (ROIs) of identical size were placed over the injection site and the axilla on both sides simultaneously and on each image in the time sequence. A similar ROI was also placed over the background (Fig. 1). ROIs were also drawn on the images showing syringes before and after injection. Thus, after subtraction of background, the counts in each ROI could be presented as a percentage of injected activity after division by the net syringe counts. Curves showing the percentage of injected activity in each axilla as a function of time after injection were generated. From these curves, the uptake in the axilla after 3 hours could be extracted. Finally, the ratio between the operated

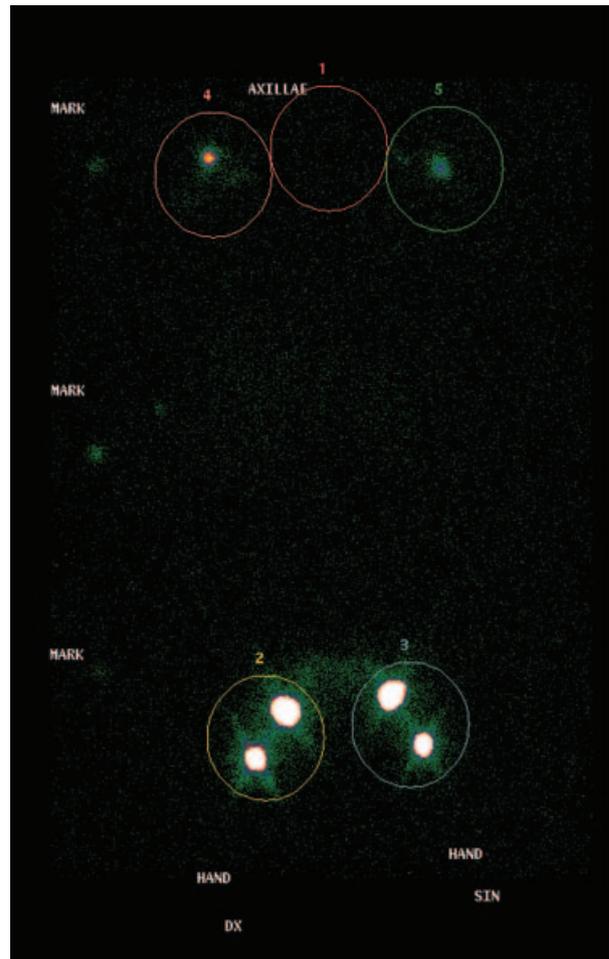


Fig. 1. Quantitative evaluation of lymphoscintigraphy with ROIs over background activity (1), injection sites (2 and 3), and axillae (4 and 5); normal findings.

and the non-operated side was calculated. The following parameters were used for quantitative analysis of tracer kinetics: clearance from the injection site, amount of indicator in the axilla compared with that in the injection site after 180 min (%), and time before 1% of the injected activity reached the axilla.

Skin circulation

Skin circulation was measured in both the operated and the contralateral arm on an area over the middle of the upper arm, using the laser Doppler fluxmeter (LDF) technique, as described elsewhere (8). The LDF value was obtained as a mean of five measuring points within a circular area with a diameter of 1 cm.

A laser Doppler fluxmeter with a differential detection system (Periflux Pf 1c; Perimed AB, Järfälla, Sweden) was used for the measurements. With this technique, monochromatic laser light broadens spectrally when scattered by moving objects such as blood cells, whereas the frequencies of light beams scattered in static structures alone are unchanged. The flowmeter output signal, measured in volts (V), is proportional to the number of blood cells multiplied by their mean velocity within the scattering volume.

Room and skin temperature

Room temperature and skin temperature on both the operated and the contralateral side were measured in an area over the middle of the upper arm using Raytek (Minitemp FS, Beijing, China), before and after ^{99m}Tc -nanocolloid clearance.

Questionnaire

Patients were asked to complete a questionnaire about any symptoms such as pain, numbness, and lymphedema in their operated arm 2–3 years after the radiotherapy.

Statistics

Differences between the two operations were evaluated with a nonparametric test for two independent groups (STATISTICA 6.1; StatSoft Inc, Tulsa, Okla., USA). A two-tailed Wilcoxon matched-pairs rank-sum test and the Wilcoxon rank test were applied to the median values of the groups, and χ^2 analyses were performed with Fisher's exact test. A test result with $P < 0.05$ was considered significant.

Results

Arm volume measurements

None of the 30 patients who had undergone SNB showed any clinical manifestation of lymphedema. Of the 30 patients operated on with ALND, six (20%) had clinical lymphedema, with an arm volume on the operated side that was $>10\%$ larger than on the non-operated side ($P < 0.01$). The increase in arm volume in the operated compared with the non-operated side amounted to 3% and was statistically significant ($P < 0.01$) in the ALND group, while the increase in the SNB group was 2% (non-significant). Volume measurements in the operated arm showed a median increase from before to after the operation of 6% in the ALND group ($P = 0.11$) compared with 0% in the SNB group (Table 2).

Lymphoscintigraphy

Visual analysis revealed that three patients, all in the ALND group, had lymphatic dysfunction manifested as a forearm dermal back flow. The dermal back flow ranged in magnitude from small and localized to circumferential involving one segment of the arm (Fig. 2). No other abnormalities were evident from the visual interpretation.

Two of these three patients also showed an increase in arm volume and were treated for lymphedema. Apart from the scintigraphic findings, the third patient (presented in Fig. 2) displayed no signs of lymphedema during a follow-up of 3 years.

The results of the quantitative analysis are presented in Tables 3–5. The parameters used for quantitative analysis of tracer kinetics were: clearance from the injection site, amount of tracer in the axilla compared with injection site, and time before 1% of the injected activity reached the axilla.

As shown in Tables 3 and 4, there were no significant differences between the operated and non-operated arm in either tracer clearance from the injection site or time taken for 1% of the injected activity to reach the axilla, irrespective of the surgical procedure (ALND or SNB). However, a

Table 2. Arm volume displacement

	ALND (n=30)	SNB (n=30)
Ratio of volume after to before, op. side	1.06 (0.11)	1.00 (0.09)
P value	0.11	0.64
Ratio of op. to non-op. volume postoperatively	1.03 (0.11)	1.02 (0.02)
P value	0.004	0.58

Data are median (interquartile range).

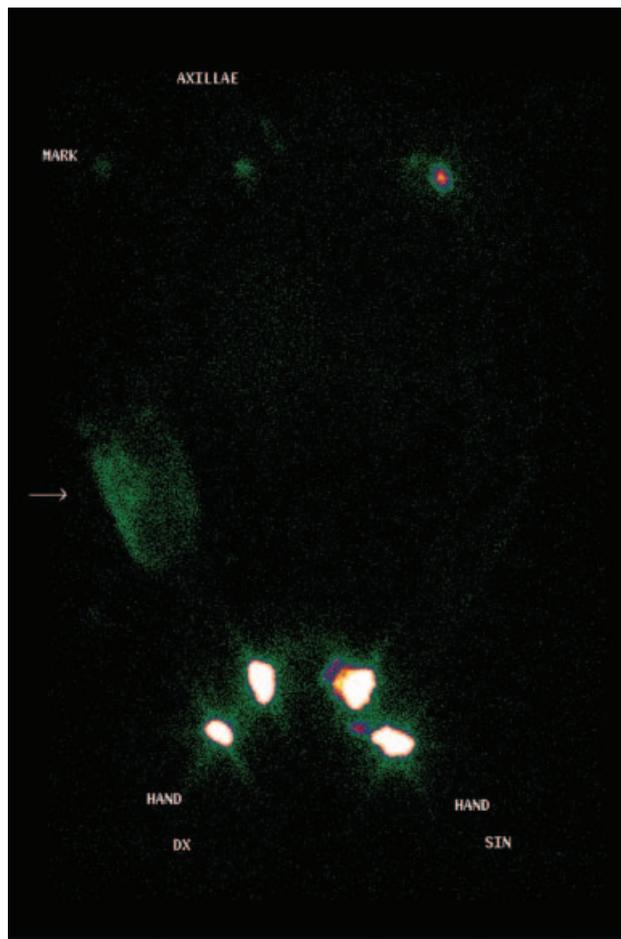


Fig. 2. Lymphoscintigraphy of patient with dermal back flow (arrow).

Table 3. Clearance of indicator from the injection site

	ALND half-time, hours (n=30)	SNB half-time, hours (n=30)
Operated side	16.1 (7.2)	15.7 (13.7)
Non-operated side	14 (8.4)	14 (14.6)
Operated/non-operated ratio	1.00 (0.77)	1.05 (0.52)
P value operated/non-operated	0.52	0.35

Data are median (interquartile range).
P value for difference between the groups=0.95.

Table 4. Time taken for 1% of the indicator to reach the axilla

	ALND, hours (n=30)	SNB, hours (n=30)
Operated side	1.35 (0.84)	1.04 (0.58)
Non-operated side	1.14 (0.54)	0.9 (0.63)
Operated/non-operated ratio	1.18 (0.73)	1.01 (0.27)
P value operated/non-operated	0.11	0.57

Data are median (interquartile range).
P value for difference between the groups=0.14.

difference was found in the maximal amount of isotope accumulated in the axilla. In patients who had undergone ALND, the amount of isotope on

Table 5. Amount of indicator in the axilla compared with the injection site after 180 min (%)

	ALND (n=30)	SNB (n=30)
Operated side	1.92 (1.90)	3.27 (2.01)
Non-operated side	3.05 (1.90)	3.28 (2.53)
Operated/non-operated ratio	0.66 (0.52)	0.96 (0.36)
P value	0.0011	0.83

P value for difference between the groups=0.0015.

the operated side was significantly smaller than on the non-operated side. No such difference was seen in the group operated on with SNB (Table 5).

Skin circulation and room temperature

Neither skin circulation (LDF) nor skin temperature, measured before and after lymphoscintigraphy on the upper arm, differed between the patients who had undergone ALND and SNB. Nor did the room temperatures differ during the measurement period (Table 6).

Questionnaire

The relative number of symptom-free patients was larger in the SNB (67%) than in the ALND group (30%) (Table 7).

Discussion

The clinical consequence of reduced lymph circulation is not clear. Lymphedema develops when the production of lymph flow exceeds the transport capacity of the tissue and leads to output failure of the lymph vascular system (17). The difference between normal transport capacity and maximum lymph flow is called the lymphatic transport reserve. It is reasonable to believe that this reserve decreases after axillary dissection, leading to reduced maximum lymph flow (17).

The implementation of modern surgical techniques in patients with breast cancer has led to fewer and milder cases of lymphedema, which can be difficult to diagnose, especially at an early stage. Undiagnosed, lymphedema can ultimately result in lipid deposition and secondary fibrosis, whereas early diagnosis and treatment often produce rapid clinical improvement and prevent progression to the chronic phase.

Our results showed that 20% of the patients in the ALND group had lymphedema, defined as an increase in arm volume >10%, compared with none in the SNB group. This is in line with the results presented by SCHRENK et al. (19) in a prospective, non-randomized study of 35 SNB

Table 6. Skin circulation measured by laser Doppler fluxmetry, skin temperature, and room temperature before and after lymphoscintigraphy.

	ALND before	ALND after	SNB before	SNB after
LDF operated side, V	7.10 (5.15)	6.40 (4.95)	7.80 (11.85)	7.00 (6.20)
LDF non-operated side, V	7.40 (3.30)	6.95 (2.95)	7.60 (6.60)	7.20 (6.65)
Operated/non-operated ratio	1.04 (0.40)	1.04 (0.42)	0.99 (0.34)	0.94 (0.35)
<i>P</i> value for difference in change between the groups=0.24.				
Skin temperature operated side, °C	31.75 (1.88)	32.50 (1.38)	32.00 (1.88)	32.25 (1.50)
Skin temperature non-operated side, °C	31.75 (2.00)	32.00 (2.25)	32.00 (1.00)	32.00 (1.50)
<i>P</i> value for difference in change between the groups=0.65.				
Room temperature, °C	22.00 (1.30)	22.30 (0.90)	22.00 (1.75)	22.10 (1.95)
<i>P</i> value for difference in change between the groups=0.58.				

Data are median (interquartile range).

Table 7. Results of questionnaire concerning symptoms such as heaviness, tension, tenderness, and swelling of the arm.

	ALND	SNB	Total
Symptoms	21	10	31
Symptom-free	9	20	29
Total	30	30	60

P value 0.0048.

patients and 35 patients undergoing ALND. They found no significant difference between preoperative and postoperative measurements of arm circumference in the SNB group, whereas a significant increase occurred in the ALND group. Their results and ours indicate that the change in volume after SNB is negligible compared with that after ALND.

The ALNB group displayed a tendency for the median arm volume to be larger after the operation than before ($P=0.11$). This is in accordance with the finding by PAIN et al. (14) of a 5.7% increase in median volume in a group of patients with a history of breast-cancer-related lymphedema, although only six of the 18 subjects fulfilled the generally accepted criterion of lymphedema as a volume increase of 10% or more.

Two common methods for determining volume in clinical practice are water displacement and circumference measurement. Earlier studies by PANI et al. and CASLEY-SMITH et al. showed a significant correlation between actual volume measured by water displacement and circumference measurements (3, 15), which some authors consider to be the "golden standard" (20).

We chose to measure arm volume by water displacement. In our study, the two arms were measured simultaneously. In this way, the arm edema volume can be monitored with the contralateral arm serving as a control, thereby avoiding an effect of variations in general body mass.

Lymphoscintigraphy as an objective diagnostic method has been used not only to diagnose and characterize the severity of lymphedema but also to

evaluate treatment results (24) and to identify patients at risk of developing lymphedema before any clinical manifestations are present (1).

The reliability of lymphoscintigraphy has been documented in numerous studies, independently of differences in investigative procedures, tracers, or interpretation. In one study, the sensitivity and specificity were found to be close to 100% using visual interpretation alone (21), while in others quantification has been used for the same purpose (2). The most frequently used quantitative parameters have been: clearance rate and uptake in lymph nodes (2, 27). It has also been reported that quantitative analysis can show inconsistent removal of the tracer from both the normal and the abnormal limb, with a significant overlap (26). It has been suggested that quantitative analysis can be useful only when the distributional pattern in the visual interpretation is not diagnostic (18). That is the reason why we evaluated our data both visually and quantitatively.

The principal advantage of a combined approach that covers several different characteristics of the lymphatic system has to do with the variety of disorders that can be present in this system. In a study by KLEINHANS et al. (10), some patients had an abnormal distribution pattern, while transport kinetics was within normal limits; in other patients, transport was delayed but the distribution pattern was normal. For this reason, mapping several different characteristics of lymphatic function improves the ability not only to establish a diagnosis of lymphedema but also to define specific anatomic details of the lymphatic system in each patient.

The qualitative analysis of lymphoscintigrams showed a pathological dermal back flow in three patients. Two of these patients had clinical signs of lymphedema requiring lymphotherapy. The third patient still had no clinical symptoms 3 years after ALND. The other four of the in total six patients with clinical lymphedema did not display any pathological dermal back flow or other pathology

in either the visual or the quantitative evaluation. Our results do not support those of earlier studies.

We chose to analyze the lymphoscintigraphy results quantitatively in terms of the elimination of isotope from the injection site, the time point at which 1% of the injected amount of the isotope reached the axilla, and the amount of isotope remaining in the axilla 180 min after the injection. The results showed no difference either in the elimination or in the time before 1% of the injected amount of the isotope reached the axilla, but the amount of isotope in the axilla 180 min after the injection was lower in the ALND group. This is simply explained by the smaller number of lymph nodes.

A change in venous return has been observed after axillary dissection (24). Svensson et al. (23) reported that no abnormalities in venous return were found in any of the unaffected contralateral arms in 81 women, whereas such abnormalities were noted in 70% of the arms affected by breast-cancer-related lymphedema. Similar abnormalities have been demonstrated in some other studies (7), but not in others (30). Lymphedema often results in histopathological changes in the skin (12). In order to evaluate dermal circulation after SNB or ALND in terms of the microcirculation, but not venous return in particular, we studied skin blood flow by using laser Doppler fluxmetry and skin temperature. No difference was found between the operated and the non-operated arm regardless of whether the patient had undergone SNB or ALND.

Fewer patients in the SNB group reported symptoms from the shoulder/arm region compared with the ALND group. This is in line with the finding by PEINTINGER et al. (16) that arm/shoulder symptoms occurred in 36% of patients after SNB compared with 68% after ALND. Similar results have been reported from other studies, with fewer symptoms from the shoulder/arm region after SNB compared with ALND (22).

One of the possible limitations of the current study is the absence of baseline lymphoscintigraphy before surgery for the evaluation of pre-existing lymphatic disorders without clinical manifestations. One such patient could be our case with dermal back flow but no objective signs of lymphedema. However, this is obviously impossible to determine retrospectively.

In conclusion, data from the current study show that lymph drainage on the operated side compared with the non-operated side is less affected by SNB than by ALND and that morbidity associated with SNB is lower than with ALND. However, the

results do not confirm our hypothesis that lymphoscintigraphy can reveal differences in lymph circulation that are not clinically evident in the form of manifest lymphedema. The most sensitive clinical method seems to be the measurement of arm volume.

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