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UPPER EXTREMITY LYMPHEDEMA AFTER AXILLARY LYMPH NODE DISSECTION: PROSPECTIVE LYMPHOSCINTIGRAPHIC EVALUATION

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ABSTRACT

This prospective study was designed to evaluate changes in upper extremity lymphatic drainage after ALND in comparison to the preoperative status using lymphoscintigraphy. The study enrolled 44 women (mean age: 57.95; range: 35-80) with a new diagnosis of unilateral invasive breast carcinoma who had been scheduled to undergo ALND. This was a substudy of the physiotherapeutic project, in which subjects after ALND were randomized into 4 groups treated with: 1) rehabilitation exercises; 2) manual lymphatic drainage; 3) pneumatic compression pump; and 4) education only. Clinical evaluation which included arm measurements and lymphoscintigraphy was performed in every subject before surgery and 3 times after surgery (1-6 weeks, 1 and 2 years after ALND). Follow-up was completed in 44 subjects at 1 year and in 32 subjects at 2 years. Lymphedema diagnosis was made in 4 subjects 1 year after ALND (9%) and in 8 subjects 2 years after ALND (25%). Among them, respectively, only 50% and 62% noticed and reported lymphedema. Quantitative analysis of lymphoscintigrams and photoplethysmography results did not reveal upper extremities lymphatic transport and/or venous function impairment after the ALND procedure. Qualitative analysis of lymphoscintigrams revealed most commonly disappearance of previously functional lymph nodes and appearance of dermal backflow in subjects who developed lymphedema. Conversely, appearance of functional lymph nodes in different locations after ALND may indicate protection from development of upper extremity lymphedema.

Keywords: breast cancer, axillary lymph node dissection (ALND), lymphedema, lymphoscintigraphy, lymphatic transport, photoplethysmography, prospective randomized control study

Arm lymphedema is a frequent complication of breast cancer therapy and affects 20-40% women with a delay of months to years after surgery. Aggressive cancer treatment may increase the risk of lymphedema (1-3). The condition is associated with a number of physical symptoms, such as pain, impaired function of the affected arm, infection, and occasionally skin malignancy. It is also a cause of psychological

morbidity (anxiety, depression, and emotional distress) that further negatively affects activities of daily living and worsens survivors' overall quality of life (4,5).

The pathophysiology of arm lymphedema after breast cancer treatment is not fully understood. Disruption of lymphatics due to axillary lymph nodes dissection (ALND) and radiation therapy are recognized as the major pathophysiological factors (6). The history of infection in the arm on the side of breast surgery and obesity are the other well recognized risk factors of breast cancer related lymphedema (3,6,7).

However, the majority of women after ALND do not develop arm lymphedema in spite of the same treatment. Assumed pathomechanisms of arm lymphedema after ALND are: deterioration of newly developed collateral circulation by fibrous scar and radiation therapy, lymphatic pump failure due to lymphatic overload, and venous hypertension caused by axillary/subclavian vein stenosis or occlusion. Conversely, protective mechanisms include: existence of additional extraaxillary lymphatic pathways and development of peripheral lymphovenous communications (8).

At this point, it is not possible to identify patients who will develop lymphedema after cancer treatment. We designed this prospective study to evaluate changes in upper extremity lymphatic drainage after ALND in comparison to the preoperative status using lymphoscintigraphy. The prospective study may lead to better understanding of pathogenesis of breast cancer related lymphedema.

MATERIAL AND METHODS

Patients

We have prospectively recruited 44 women (mean age: 57.95; range: 35-80) with a new diagnosis of unilateral invasive breast carcinoma who were scheduled to undergo operation, including ALND. ALND was performed by an experienced team of oncological surgeons. The standard surgical procedure has been fully described previously (9). In brief, regardless of the clinical axillary lymph node (ALNs) status, the removal of levels I, II and III nodal tissue in one bloc was performed in every case. The axillary vein was the upper limit of the range of surgery and the posterior wall of the axilla (including subscapularis, latissimus dorsi and teres major muscles) was clearly seen during each surgery.

The subjects enrolled into our study were the participants in a larger physiotherapeutic project and agreed to have additional lymphoscintigraphies according to our protocol. All recruited subjects were randomized into one of 4 groups regarding physiotherapy after ALND: 1) rehabilitation exercises (n=11); 2) manual lymphatic drainage (n=16); 3) pneumatic compression pump (n=12); and 4) educational program only (n=5). The subjects were followed for two years after ALND. The physiotherapy program was initiated one day after the surgery and conducted 5 times a week for 4 weeks. If lymphedema was diagnosed in a participating subject, immediate decongestive lymphatic therapy (DLT) including compression, manual lymphatic drainage, pneumatic pump, and skin care was initiated.

The study was approved by the Local Bioethical Committee of the Wroclaw Medical University and all subjects gave informed written consent prior to inclusion in the study. Selected demographic and medical parameters are presented in *Table 1*.

Study Design

The study protocol for all subjects included: physical examination, measurements of both upper limbs circumferences in 4 cm intervals, lymphoscintigraphy, and photoplethysmography. Evaluation was performed before surgery, 1-6 weeks after surgery, and 1, and 2 years later.

Lymphedema diagnosis in our subjects was made when both of the following

TABLE 1
Demographic and Medical Parameters of the Subjects

	1 year after ALND (n=44)		2 years after ALND (n=32)	
Parameter	**Women with lymphedema (n=4)**	**Women without lymphedema (n=40)**	**Women with lymphedema (n=8)**	**Women without lymphedema (n=24)**
Age before ALND (years) mean / range	58 / 52-62	57.95 / 35-80	57.5 / 49-65	58.63 / 35-74
BMI (kg/m^2)				
before ALND mean	32.9	26.6	29.1	26.9
1 - 2 years after ALND mean	32.9	26.6	29.7	26.8
Type of surgery				
total mastectomy	3 (75%)	25 (62.5%)	6 (75%)	14 (58.3%)
breast-conserving surgery	1 (25%)	15 (37.5%)	2 (25 %)	10 (41.7%)
Breast cancer				
right sided	2 (50%)	23 (57.5%)	3 (37.5%)	13 (54.2%)
left sided	2 (50%)	17 (42.5%)	5 (62.5%)	11 (45.8%)
Adjuvant therapy				
Radiation therapy	2 (50%)	13 (32.5%)	4 (50%)	7 (29.2%)
Chemotherapy	4 (100%)	14 (35%)	5 (62.5%)	8 (33.3%)
Hormone therapy	3 (75%)	24 (60%)	7 (87.5%)	16 (66.7%)
Diagnosis of diabetes	0 (0%)	4 (10%)	0 (0%)	4 (16.7%)
Diagnosis of hypertension	4 (100%)	19 (47.5%)	7 (87.5%)	11 (45.8%)
Upper extremity subjective symptoms on the cancer side 1-2 years after ALND				
Pain	2 (50%)	14 (35%)	4 (50%)	8 (33.3%)
Function impartment	2 (50%)	13 (32.5%)	3 (37.5%)	9 (37.5%)
Subjective edema	2 (50%)	9 (22.5%)	5 (62.5%)	5 (20.8%)
Physiotherapeutic groups				
1 - rehabilitation exercises	0 (0%)	11 (27.5%)	1 (12.5%)	8 (33.3%)
2 - manual lymphatic drainage	3 (75%)	13 (32,5%)	4 (50%)	9 (37.5%)
3 – pneumatic compression pump	1 (25%)	11 (27.5%)	3 (37.5%)	6 (25%)
4 - education only	0 (0%)	5 (12.5%)	0 (0%)	1 (4.2%)

diagnostic criteria were fulfilled: 1) upper extremity circumference measurements were measured at 4 cm distance: the upper limb edema was defined as at least 2.0 cm circumference difference increase at minimum 2 arm levels, and 2) upper extremity edema volume

increase: the upper limb edema was defined as at least 200 ml difference between operated arm and not operated arm, adjusted for the pre-op difference between arm volumes. Arm volume was calculated from arm circumferences measured at 4 cm distances using the formula for a truncated cone (10).

Lymphoscintigraphy

Bilateral subcutaneous injection of 0.25 mCi of 99mTc-Nanocoll was performed simultaneously in both hands in the second and the third interdigital space (total dose per subject amounted 1mCi).

Static acquisitions were obtained 10 minutes and 2 hours after the injection. This procedure was performed preoperatively and was repeated further 3 times: 1-6 weeks, 1 year and 2 years after the surgery.

ALNs status before and after ALND was evaluated in every subject qualitatively and quantitatively.

Qualitative analysis was performed for every patient independently by two physicians. The patients were divided into the following groups:

(1) disappearance of previously functional lymph nodes,

(2) appearance of dermal backflow (accumulation of the radiotracer within the subcutis/skin),

(3) lymph nodes seen in the same localization,

(4) lymph nodes seen in the same and additionally in different locations,

(5) lymph nodes seen in different locations, and

(6) lymphocele.

For quantitative analysis, symmetrical regions of interest (ROIs) were placed over the injection site and over the axilla on each lymphoscintigram. Radioactivity in ROIs were measured 10 minutes after injection (ROI^{0}) and 2 hours later (ROI^{2h}), before and after ALND.

Quantification of lymphatic transport was performed by calculation for each upper extremity before and 3 times after surgery (1-6 weeks, 1 year, and 2 years after ALND) the following parameters:

(1) Axillary ratio 2 hours post injection (AR^{2h}): the radioactivity was measured at ROI over axilla 2 hours post injection ($ROI_{ax.}$) to radioactivity of symmetrical ROI over injection site ($ROI_{inj.}$) for each upper extremity before and 3 times after surgery by using the formula: $AR^{2h} = (ROI_{ax.} / ROI_{inj.})$;

(2) AR^{2h} ratio = AR^{2h} operated arm / AR^{2h} non-operated arm was calculated for every subject before and 3 times after ALND;

(3) Tracer disappearance rate from the injection site 2 hours post injection (TD^{2h}): the radioactivity was measured at ROI over both sites of injection ($ROI_{inj.}$) for each upper extremity before and 3 times after ALND by using the formula: $TD^{2h} = (ROI_{inj.}{}^{0} / ROI_{inj.}{}^{2h})$;

(4) Tracer disappearance ratio (TD^{2h} ratio) = TD^{2h} operated arm / TD^{2h} non-operated arm was calculated for every patient before and 3 times after ALND.

Photoplethysmography

Venous photoplethysmography was performed to evaluate the effect of ALND on venous flow in the upper extremities. Venous photoplethysmography of upper limbs was performed with Rheo Dopplex II PPG (HNE Medical) in subjects before and after ALND on the days of lymphoscintigraphy. Examination was performed in the sitting position with upper extremities allowed to hang down. The photoplethysmographic sensor was placed on the dorsal side of the wrist and the subjects then performed 10 rhythmical elbow flexions. The photoplethysmographic curve was recorded during the exercises. The venous pump index (Vp) and venous refilling time (RT) were automatically calculated using software provided by manufacturer (HNE Medical Inc.).

Statistical Methods

TABLE 2
Lymphoscintigraphic Features in Women With and Without Lymphedema

Parameter	1 year after ALND (n=44)		2 years after ALND (n=32)	
	Women with lymphedema (n=4)	Women without lymphedema (n=40)	Women with lymphedema (n=8)	Women without lymphedema (n=24)
Disappearance of previously functional lymph nodes	2 (50%)	6 (15%)	3 (37.5%)	1 (4.2%)
Appearance of dermal backflow	1 (25%)	7 (17.5%)	3 (37.5%)	3 (12.5%)
Lymph nodes present in the same localization after ALND	1 (25%)	20 (50%)	3 (37.5%)	11 (45.8%)
Lymph nodes in the same and additionally in different localization	1 (25%)	2 (5%)	2 (25%)	0 (0%)
Lymph nodes in different localization	0 (0%)	14 (35%)	1 (12.5%)	13 (54.2%)
Lymphocele	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)

Statistical analysis was performed using Statistica for Windows 12. Differences between lymphoscintigraphic and photoplethysmographic parameters before and after ALND were evaluated using t-test for dependent samples. Comparisons of quantitative parameters of lymphoscintigrams in subjects with and without lymphedema were evaluated using t-test for independent samples. Differences were considered significant when p was < 0.05.

RESULTS

Follow-up has been at 1 year for 44 subjects and at 2 years for 32 subjects. 2 subjects died and 10 withdrew their consent prior to the 2 years follow-up visit.

Lymphedema was diagnosed on the basis of circumferential measurements in 4 subjects at 1 year after ALND (9%) and in 8 subjects at 2 years after ALND (25%). Among them, only 50% (2/4) 1 year after ALND and 62% (5/8) 2 years after ALND were aware of own lymphedema.

Qualitative analysis of lymphoscintigrams revealed that disappearance of previously functional lymph nodes and appearance of dermal backflow 1 or 2 years after ALND were the lymphoscintigraphic features more frequently present in subjects with lymphedema. 1 year after ALND, ALNs were visualized in 36 of 40 examined breast cancer survivors without lymphedema (90%) in comparison to 2 of 4 breast cancer survivors with lymphedema (50%). 2 years after ALND, ALNs were visualized on lymphoscintigrams in all examined breast cancer survivors without lymphedema (100%) in comparison to 6 of 8 breast cancer survivors with lymphedema (75%). *Table 2* presents the lymphoscintigraphic features observed in lymphoscintigrams in subjects with and without lymphedema 1 and 2 years after ALND.

Analysis of lymphoscintigrams performed 1-6 weeks after ALND in subjects

TABLE 3
Lymphoscintigraphic Features in Women With and Without History of Adjuvant Chemotherapy

Parameter	1 year after ALND (n=44)		2 years after ALND (n=32)	
	Women after chemotherapy (n=18)	Women without chemotherapy (n=26)	Women after chemotherapy (n=13)	Women without chemotherapy (n=19)
Disappearance of previously functional lymph nodes	4 (22.2%)	4 (15.4%)	3 (23%)	1 (5.3%)
Appearance of dermal backflow	5 (27.8%)	3 (11.5%)	4 (30.7%)	2 (10.5%)
Lymph nodes present in the same localization after ALND	8 (44.4%)	13 (50%)	6 (46.2%)	8 (42.1%)
Lymph nodes in the same and additionally in different localization	2 (11.1%)	1 (3.8%)	1 (7.7%)	1 (5.3%)
Lymph nodes in different localization	5 (27.8%)	9 (34.6%)	4 (30.7%)	10 (52.6%)
Lymphocele	1 (5.6%)	0 (0%)	0 (0%)	0 (0%)

TABLE 4
Lymphoscintigraphic Features in Women With and Without History of Adjuvant Radiotherapy

Parameter	1 year after ALND (n=44)		2 years after ALND (n=32)	
	Women after radiotherapy (n=15)	Women without radiotherapy (n=29)	Women after radiotherapy (n=11)	Women without radiotherapy (n=21)
Disappearance of previously functional lymph nodes	5 (33.3%)	3 (10.3%)	4 (36.4%)	0 (0%)
Appearance of dermal backflow	6 (40%)	2 (6.9%)	5 (45.5%)	1 (4.8%)
Lymph nodes present in the same localization after ALND	5 (33.3%)	16 (55.2%)	4 (36.4%)	10 (47.6%)
Lymph nodes in the same and additionally in different localization	1 (6.7%)	2 (6.9%)	0 (0%)	2 (9.5%)
Lymph nodes in different localization	5 (33.3%)	9 (31%)	4 (36.4%)	10 (47.6%)
Lymphocele	0 (0%)	1 (3.4%)	0 (0%)	0 (0%)

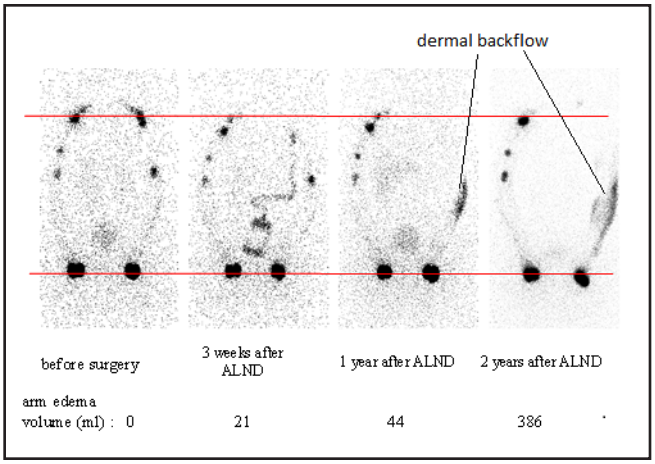

Fig. 1. Lymphoscintigrams of a subject who developed lymphedema (case 1). Lymphoscintigraphy prior to the surgery reveals symmetric axillary lymph nodes. 3 weeks after left ALND, no axillary lymph nodes (ALNs) on the left side were seen and draining set filled with tracer/lymph. 1 and 2 years after surgery no ALNs are visualized on the operated side and accumulation of the radiotracer within the subcutis/skin ("dermal backflow") is present. Arm edema (lymphedema) became evident at 2 years.

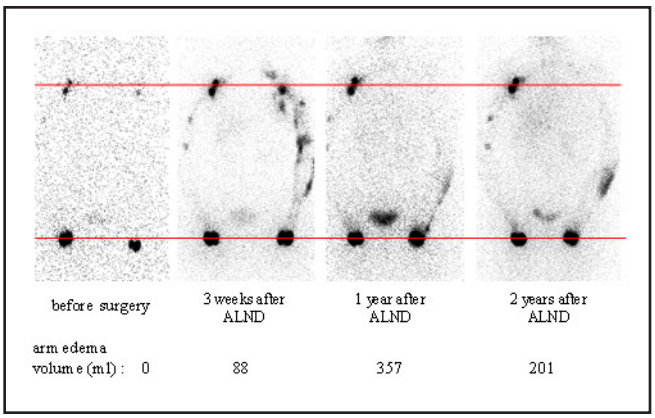

Fig. 2. Lymphoscintigrams of a subject with lymphedema (case 2). Prior to the surgery weak and slightly asymmetric visualization of ALNs. Three weeks after left side ALND, patchy and diffuse accumulation of radiotracer is seen in the arm on the operated side consistent with acute lymphedema (although still minimal volume change). 1 and 2 years after surgery, no ALNs are visualized on the operated side and accumulation of the radiotracer within the subcutis/skin ("dermal backflow") is present with measurable arm edema (lymphedema).

who developed lymphedema 1 or 2 years after ALND (n=8) and subjects without upper extremity lymphedema 1 or 2 years after ALND (n=36) revealed the following features on postoperative lymphoscintigrams associated with development of lymphedema after 1-2 years: (1) appearance of dermal backflow [in 2 subjects with lymphedema (25%) and in 1 subject without lymphedema (2.7%)]; (2) presence of lymph nodes in the same and additional different locations [in 2 subjects with lymphedema (25%) and in 4 subjects without lymphedema (11.1%)]; and (3) lymphocele [in 2 subjects with lymphedema (25%) and in 5 subjects without lymphedema (13.9%)].

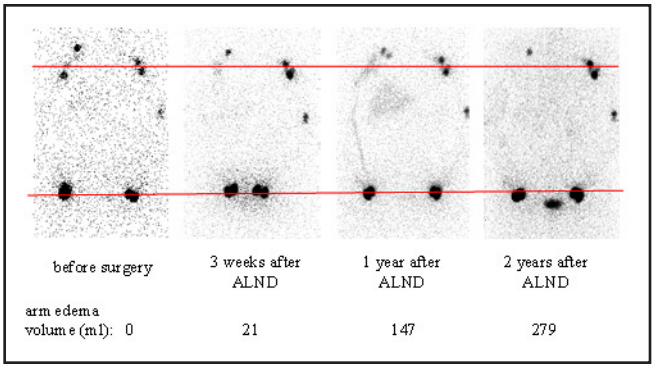

Fig. 3. Lymphoscintigrams of a subject with lymphedema (case 3). Prior to surgery, slightly asymmetric visualization of ALNs is seen. Three weeks after right side ALND, a proximal lymph node (possibly supraclavicular) is visualized. 1 and 2 years after surgery, a supraclavicular LN is visualized on the operated side and slight accumulation of the radiotracer within the subcutis/skin ("dermal backflow") is present with arm edema (lymphedema) at 2 years.

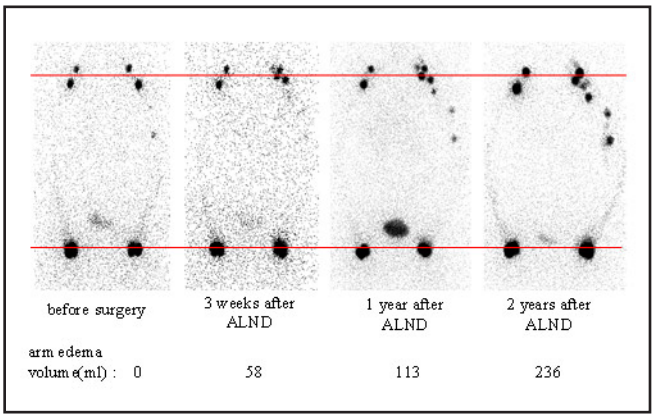

Fig. 4. Lymphoscintigrams of a subject with lymphedema (case 4). Prior to the surgery, symmetric visualization of ALNs is seen. Three weeks after left side ALND, axillary LNs are still visualized. 1 and 2 years after surgery axillary LNs are still visualized. At 2 years after ALND, intercalated LNs on the operated side are better visualized, there is slight accumulation of the radiotracer within the subcutis/skin ("dermal backflow") and measurable arm edema (lymphedema).

Presence of lymph nodes in the same location (seen in the group with lymphedema in 5 subjects (62.5%) and in the group without lymphedema in 24 subjects (66.7%)) was not associated with future lymphedema diagnosis. Both lack of any lymph node visualization without lymphocele and lymph nodes only seen in different locations were rarely seen on early lymphoscintigrams (not present in subjects with lymphedema and, respectively in 1 subject and 2 subjects in the group without lymphedema).

***Tables 3 and 4* presents the lymphoscintigraphic features observed in lymphoscintigrams 1 and 2 years after ALND in subjects with and without history of application of adjuvant chemo- and radiotherapy.**

***Figs. 1-4* present the examples of lymphoscintigraphic alterations that are present more often in subjects with lymphedema. *Fig. 5* shows the example of lymphoscintigram in women without lymphedema.**

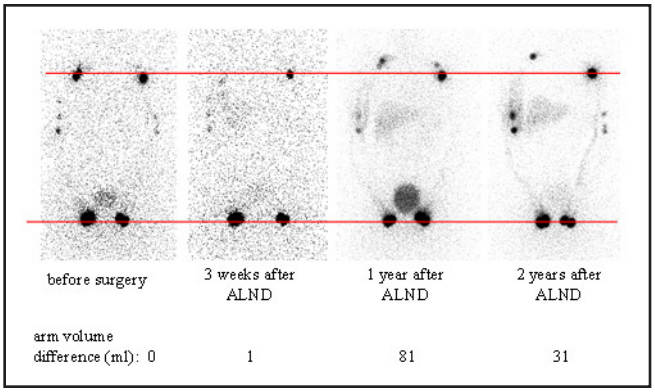

Fig. 5. Lymphoscintigrams of a subject without lymphedema (case 5). Prior to the surgery, symmetric visualization of ALNs is seen. Three weeks after right side ALND, no ALNs are visualized on the operated side. 1 and 2 years after surgery, a supraclavicular LN is visualized on the operated side and arm edema is not present.

TABLE 5
Differences Between Lymphoscintigraphic Axillary Ratio (AR2h) and Tracer Disappearance Rate (TD2h) Before and After ALND

	Mean	Difference	p value
AR^{2h} ratio 1 vs. AR^{2h} ratio 2	1.21 vs.1.01	0.20	0.069
AR^{2h} ratio 1 vs. AR^{2h} ratio 3	1.19 vs 0.97	0.22	0.123
AR^{2h} ratio 1 vs. AR^{2h} ratio 4	1.15 vs 0.86	0.29	0.067
TD^{2h} ratio 1 vs. TD^{2h} ratio 2	0.99 vs.1.01	- 0.02	0.390
TD^{2h} ratio 1 vs. TD^{2h} ratio 3	0.99 vs. 1.01	- 0.02	0.176
TD^{2h} ratio 1 vs. TD^{2h} ratio 4	0.99 vs. 1.00	0.01	0.787

AR^{2h} ratio 1-4: lymphoscintigraphic axillary ratio operated/not operated arm accordingly: AR^{2h} ratio 1 - before ALND; AR^{2h} ratio 2 - 1-6 weeks after ALND; AR^{2h} ratio 3 - 1 year after ALND; AR^{2h} ratio 4 - 2 years after ALND; TD^{2h} ratio 1-4: tracer disappearance rate operated/not operated arm accordingly: TD^{2h} ratio 1 - before ALND; TD^{2h} ratio 2 - 1-6 weeks after ALND; TD^{2h} ratio 3 - 1 year after ALND; TD^{2h} ratio 4 - 2 years after ALND.

Quantitative analysis of lymphoscintigrams revealed that the lymphatic transport from the upper extremities was not affected by the ALND procedure. *Table 5* displays no statistical difference in lymphoscintigraphic axillary ratio and tracer disappearance rate ratio (AR^{2h} ratio and TD^{2h} ratio) before and after ALND. *Table 6* demonstrates the comparison of AR^{2h} ratio and TD^{2h} ratio in subjects with and without lymphedema. These differences ware also statistically not significant.

Photoplethysmography results also show that venous function was not affected by the surgery. *Table 7* presents the values of venous pump index (Vp) and venous refill time (RT) of the upper extremity on the operated side. They did not differ statistically relevantly before and after ALND.

TABLE 6
Comparison of AR^{2h} and TD^{2h} in Women With and Without Lymphedema

Parameter	1 year after surgery			2 years after surgery		
	Women with lymphedema (n=4)	Women without lymphedema (n=40)	p value	Women with lymphedema (n=8)	Women without lymphedema (n=24)	p value
AR^{2h} ratio 1	1.15	1.61	0.140	1.38	1.12	0.273
AR^{2h} ratio 2	0.94	1.71	0.084	1.24	0.80	0.216
AR^{2h} ratio 3	0.99	0.84	0.702	0.82	0.98	0.576
AR^{2h} ratio 4	-	-	-	0.89	0.82	0.783
TD^{2h} ratio 1	0.99	0.97	0.679	0.99	1.00	0.887
TD^{2h} ratio 2	1.00	1.04	0.323	1.02	1.00	0.369
TD^{2h} ratio 3	1.01	1.01	0.927	1.01	1.01	0.960
TD^{2h} ratio 4	-	-	-	0.98	1.00	0.590

AR^{2h} ratio 1-4: lymphoscintigraphic axillary ratio operated/not operated arm accordingly: AR^{2h} ratio 1 - before ALND; AR^{2h} ratio 2 - 1-6 weeks after ALND; AR^{2h} ratio 3 - 1 year after ALND; AR^{2h} ratio 4 - 2 years after ALND; TD^{2h} ratio 1-4: tracer disappearance rate operated/not operated arm accordingly: TD^{2h} ratio 1 - before ALND; TD^{2h} ratio 2 - 1-6 weeks after ALND; TD^{2h} ratio 3 - 1 year after ALND; TD^{2h} ratio 4 - 2 years after ALND.

TABLE 7
Photoplethysmography Results: Venous Pump Index and Venous Refill Time of the Upper Extremity on the Operated Side Before and After ALND

	mean	difference	p value
Vp 1 vs. Vp 2	33.14 vs.32.41	0.73	0.841
Vp 1 vs. Vp 3	35.17 vs 30.79	4.38	0.349
Vp 1 vs. Vp 4	37.12 vs 38.06	0.94	0.864
RT 1 vs. RT 2	16.84 vs. 20.62	- 3.78	0.156
RT 1 vs. RT 3	17.00 vs. 19.93	-2.93	0.399
RT 1 vs. RT 4	15.05 vs. 23.41	-8.35	0.060

Vp - venous pump index. accordingly: Vp 1 - before ALND; Vp 2 - 1-6 weeks after ALND; Vp 3 - 1 year after ALND; Vp 4 - 2 years after ALND; RT - venous refill time. accordingly: RT 1 - before ALND; RT 2 - 1-6 weeks after ALND; RT 3 - 1 year after ALND; RT 4 - 2 years after ALND.

DISCUSSION

In this prospective study, the overall incidence of objectively diagnosed lymphedema at 1-2 years after ALND was 9% and 25%, which is consistent with other reports (1-3). Circumference difference above 2 cm at minimum 2 arm levels and upper extremity edema volume increase of at least 200 ml were our cut-off point for the diagnosis of lymphedema. Dominant arms can be naturally up to 2 cm in circumference and 200 ml in volume greater that non-dominant (11-13). Unlike in the majority of studies, we included arm measurements before surgery to our study protocol. This way we were able to control and recognize a truer increase of upper extremity circumference and volume due to operation and adjuvant treatment.

The incidence of lymphedema based on objective measurements in many cases does not reflect the prevalence of lymphedema reported by affected women. In our study, only half of the subjects from lymphedema group after 1 year after ALND and 62.5% of women after 2 years after ALND reported to have arm edema. On the other hand, approximately 20% of subjects in the group without lymphedema diagnosed using our criteria complained to suffer from this condition. Subjects in the group with lymphedema more frequently complained of upper extremity pain and functional impartment, which is in agreement with published reports on disability and lymphedema (4,5).

Subjects with lymphedema in our study had greater BMI, more frequently history of hypertension, history of radical mastectomy and adjuvant therapy (radiotherapy, chemotherapy, hormone therapy), which is also in agreement with other studies on lymphedema risk factors (2,6,7,14).

Removal of a greater number of lymph nodes during ALND is the most important risk factor of lymphedema. It can be explained by the greater disruption of upper extremity lymphatic drainage pathways during more extensive axillary surgery. The sentinel lymph node biopsy (SLNB) lowers the incidence of lymphedema to the level of 3-7%. Recent studies demonstrated that the removal of more than 5 axillary lymph nodes significantly increases the risk of lymphedema. After the removal of 10 or more lymph nodes, the prevalence of arm lymphedema increases in an approximately linear manner (3,14,15). Removal of up to five lymph nodes has been suggested to be safe with respect to lymphedema (16). However, Britton et al. demonstrated that in 13 of 15 women, lymphatic drainage from upper extremity and from the breast were separated but in the other 2 of 15 patients, sentinel lymph node (SLN) was joint (17). Patients with SLN within the common lymphatic drainage pathway for breast and upper extremity may be at increased risk of developing lymphedema after ALND.

In our study, ALNs after ALND were visualized significantly more often on lymphoscintigrams in breast cancer survivors without lymphedema in comparison to subjects with this complication, and this finding may indicate a protective effect against lymphedema. This supports our earlier findings in which the presence of functional ALNs seen by lymphoscintigraphy in subjects after breast cancer surgery and ALND was associated with lower frequency of lymphedema development (18). Presence of ALNs after ALND may be due to a lower number of nodes resected during surgery. However, recent studies confirm that ALNs that remain after ALND are not the ones that were missed during the surgery. Their presence is rather a natural consequence of classic surgical technique of level I+II+III ALND procedure that does not allow removal of all ALNs in the majority of operated subjects. There may also be a hereditary predisposition to breast cancer related lymphedema development, provided, that is, by individual anatomical arrangement of axillary lymph nodes (9,16).

Early lymphedema may develop without lymphoscintigraphic evidence of impaired

lymphatic drainage. However, our study shows that there are some characteristic lymphoscintigraphic features that are present more often in subjects with lymphedema diagnosis. Disappearance of previously functional lymph nodes and appearance of dermal backflow seem to correlate with lymphedema development. Conversely, presence of lymph nodes in different localization after surgery seems to indicate a protective effect. Their presence could be a reflection of collateral lymphatic pathways which were recruited, and they may be seen as a compensatory mechanism after impairment of axillary lymphatic system.

We were also searching for characteristic features of lymphoscintigrams performed early after ALND that may help predict development of lymphedema 1 or 2 years after surgery. This analysis indicates that dermal backflow, presence of lymph nodes in the same and additionally in different locations, and lymphocele were more common in women who developed lymphedema after 1 and 2 years.

Our study also indicates that history of adjuvant chemotherapy and radiotherapy is associated with similar lymphoscintigraphic features as lymphedema onset, i.e., disappearance of previously functional lymphnodes and appearance of dermal backflow.

Taking into account that subjects who were enrolled in our study were the participants in the rehabilitation project, the prevalence and severity of lymphedema might be lower than in the average population of breast cancer survivors. Different types of rehabilitation may influence lymph drainage and lymphoscintigraphic patterns. Unfortunately, our subgroups were too small to examine these data. Published studies have demonstrated that physiotherapy treatment improves upper extremity function after ALND. It also helps to identify presence of lymphedema at its earliest stage, and early treatment prevents progression to the chronic phase of the disease, associated with fibrosis and lipid deposition in the subcutaneous tissue that is more difficult to treat (19).

CONCLUSIONS

Our study shows that pre- and post-surgical lymphoscintigraphy cannot predict the risk of lymphedema development. However, we have found some characteristic lymphoscintigraphic features that are present more often in subjects who developed lymphedema. Disappearance of previously functional lymph nodes and appearance of dermal backflow seems to be associated with lymphedema development. In contrast, presence of lymph nodes in different localization after ALND may indicate some protection from lymphedema development.

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