Lymphology 40 (2007) 81-86

PRESENCE OF FUNCTIONAL AXILLARY LYMPH NODES AND LYMPH DRAINAGE WITHIN ARMS IN WOMEN WITH AND WITHOUT BREAST CANCER-RELATED LYMPHEDEMA

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ABSTRACT

This pilot study was designed to investigate lymphatic transport in the arms of women after breast cancer treatment without lymphedema and with mild and severe arm lymphedema. Nineteen breast cancer survivors [6 without (Group 1), 6 with mild (Group 2) and 7 with severe (Group 3) lymphedema] were examined. Lymphatic transport in the arm and to axillary lymph nodes were evaluated using quantitative radionuclide lymphscintigraphy. The radioactivity ratio between the operated and unoperated axillae (axillary ratio), and both lymphatic transport and tracer disappearance rates (TDR) from the injection sites were calculated. We found that axillary ratio and lymphatic transport were significantly higher in Groups 1 and 2 compared to 3 and that TDR was not affected in any Group. Additionally, lymphscintigraphy revealed presence of functional axillary lymph nodes within the operated axilla in women without or with mild lymphedema, while in women with severe lymphedema, no axillary lymph nodes were visualized. We conclude from our subjects that breast cancer survivors who did not develop or had mild arm lymphedema have functional lymphatic transport and lymph nodes in the axillary area on the operated side. This suggests that efficient collateral circulation and/or peripheral lymphovenous communications has developed in these subjects which may be preventative for the development of severe lymphedema.

Keywords: breast cancer-related lymphedema, lymph node dissection, axillary clearance, radiotherapy, lymphscintigraphy, lymph flow

Axillary lymph node dissection during breast cancer surgery often results in development of arm lymphedema, termed in the literature "breast cancer-related lymphedema." Arm lymphedema affects about one-third of all breast cancer survivors and may develop as early as a few weeks up to many years after breast cancer treatment (1). Axillary surgery and irradiation to the axilla are recognized as the major risk factors for this complication. Other described factors that predispose to developing this complication are hypertension, obesity, and increased age. However, pathophysiology of breast cancer related lymphedema is not well understood (2-4).

Delay in return of interstitial fluid to the general circulation is thought to be the main failure leading to lymphedema, and axillary lymph node dissection, resulting in disruption of vessels draining the arm, is assumed to be the key event in the development of arm lymphedema after breast cancer treatment. However, arm lymphedema following breast cancer treatment is a complex, multifactorially determined condition, the pathophysiology of lymphedema in the view of recent studies is still not well understood, and the proposed mechanisms leading to the development of arm lymphedema are still largely hypothetical. The question why arm lymphedema does not affect the majority of breast cancer survivors is challenging.

Lymphscintigraphy remains the gold standard of lymphatic system evaluation. The most characteristic lymphscintigraphic features of lymphedema include dilated and/or tortuous lymph vessels, delayed tracer disappearance rate from the injection site, lack of visualization of regional lymph nodes, and presence of "dermal backflow" (5-7).

The aim of our pilot study was to investigate whether lymphatic transport in the arm and, therefore, functional lymphatic anatomy in women after breast cancer treatment differs among Groups without lymphedema, and with mild and severe lymphedema.

MATERIALS AND METHODS

Subjects

The study group consisted of 19 women aged 47-76 years (mean 60.0) from the Breast Cancer Survivor Support Group "Amazonki." All women underwent surgical treatment for breast cancer (mastectomy + axillary lymph node dissection). The time from surgery ranged between 1 and 16 years (average 6.6 years). Radiation therapy as an adjuvant treatment was performed in 11 and chemotherapy in 9 women.

The subjects were divided into three groups. The first group (Group 1) consisted of 6 women with no arm lymphedema. The second group (Group 2) consisted of 6 women with intermittent, mild lymphedema (1st stage). The arm circumference difference at any level was less than 2 cm in this group. The third group (Group 3) consisted of 7 women with permanent, severe arm lymphedema (stage II with arm circumference difference >2 cm). Selected demographic and treatment parameters for groups are presented in *Table 1*.

The study was approved by the Bioethical Committee at Wroclaw Medical University, and all subjects gave informed written consent prior to inclusion in the study.

Lymphscintigraphy

Lymphatic transport in the arm and axillary lymph node visualization were evaluated using quantitative radionuclide lymphscintigraphy. 0.25 mCi of 99mTc-Nanocoll was injected subcutaneously in two interdigital spaces of each hand. Total dose amounted to 1 mCi per subject. Quantification of lymphatic transport was estimated by analyzing the regions of interest (ROI). Symmetrical ROIs were placed over the injection sites and over the axilla on each lymphscintigram (*Fig. 1*). Radioactivity in ROIs was measured immediately after injection (ROI^0) and 2 hours later (ROI^{2h}). Quantification of lymphatic transport was done by evaluation in each ROI following parameters:

(1) Axillary ratio 2 hours post-injection (AR^{2h}). Radioactivity was measured at ROI over both axillae 2 hours post-injection and the ratio of the operated to non-operated side on each lymphscintigram was calculated, i.e., for *Fig. 1*, the axillary ratio would be: $AR^{2h} = ROI^c / ROI^d$.

(2) Lymphatic transport to axillary area 2 hours post-injection (LT^{2h}) was measured as total radioactivity at axilla ROI 2 hours post-injection.

(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 by using the formula:

TD^{2h} (%) = $(ROI^0 - ROI^{2h}) / ROI^0$; i.e., for *Fig. 1*. TD^{2h} of both sides would be:

TD^{2h} (%) operated side = $(ROI^{b\,0} - ROI^{b\,2h}) / ROI^{b\,0}$

TD^{2h} (%) healthy side = $(ROI^{a\,0} - ROI^{a\,2h}) / ROI^{a\,0}$

TABLE 1
Demographic and Treatment Parameters of the Subjects

	Group 1 (no lymphedema)	Group 2 (stage I)	Group 3 (stage II)
Number of women	6	6	7
Mean age (years) [range]	55.2 [47-66]	59.7 [52-72]	64.6 [52-76]
Mean time from surgery (years) [range]	9.6 [1-16]	7.5 [2-14]	5.1 [3-12]
Radiation therapy (number of women)	1	3	7*
Chemotherapy (number of women)	1	2	6*

*significant difference

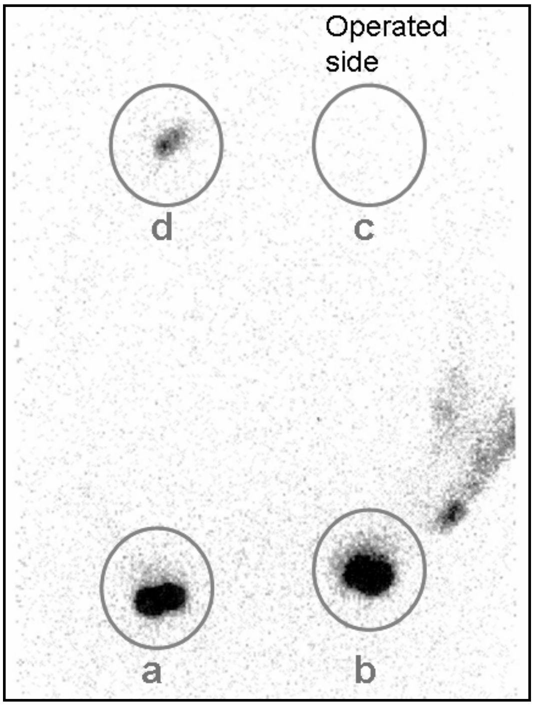

Fig. 1. Lymphscintigraphy in post-mastectomy lymphedema. Placement of regions of interest (ROIs): over the injection sites (a,b) and over the axillae (c,d).

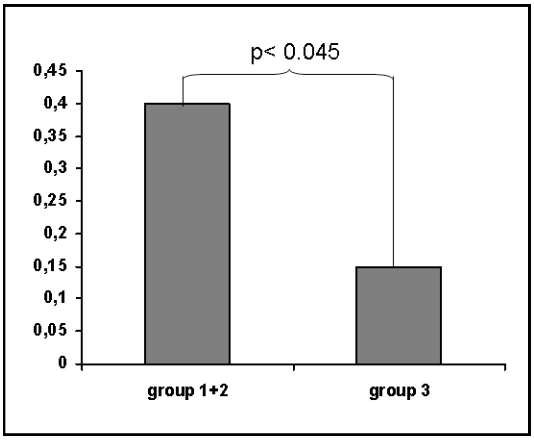

Fig. 2. Axillary ratio 2 hours post injection (AR^{2h}) comparing Groups 1+2 with 3.

Statistical analysis

Statistical analysis was performed using Statistica for Windows 6.0. Differences between lymphscintigraphic axillary ratio (AR^{2h}), lymphatic transport to axillary area (LT^{2h}) and tracer disappearance rate from

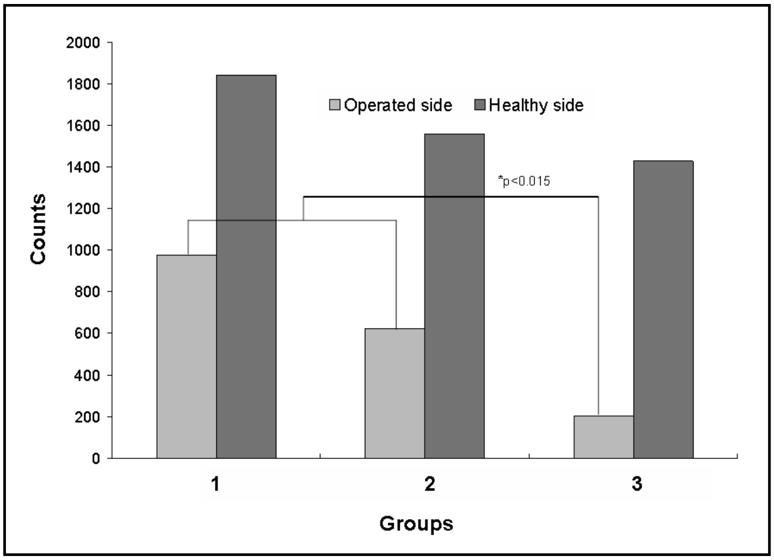

Fig. 3. Lymphatic transport to the axillary area (LT^{2h}) of both arms for subjects in Groups 1, 2, and 3. LT^{2h} was significantly reduced comparing operated to healthy side for all subjects, within all groups, and was significantly lower comparing Group 3 to Groups 1+2 ($p<0.015$) as well as Group 3 to Group 2 ($p<0.05$).

the injection site (TD^{2h}) in studied groups were evaluated with a Student t-test. Differences were considered significant when $p<0.05$.

RESULTS

Axillary ratio 2 hours post-injection (AR^{2h}) was significantly higher in Groups 1 and 2 compared to Group 3 (4.0 in Groups 1+ 2 combined vs 0.15 in Group 3; $p<0.045$) (*Fig. 2*).

Overall lymphatic transport (LT^{2h}) to the axilla was significantly lower ($p<0.001$) on the operated side (579±632, mean±S.D.) compared to the healthy side (1,520±795) in all subjects and within each group. A significantly lower ($p<0.015$) transport was found in subjects with severe lymphedema (Group 3) (203±102) in comparison to Groups 1 and 2 with no or mild lymphedema combined (799±711) and interestingly, also between Groups 2 and 3 (623±515 vs 203±102; $p<0.05$). This finding is reflected in the lymphscintigraphic presence of functional axillary lymph nodes on the operated side in women with no or with mild lymphedema (*Fig. 3*).

The tracer disappearance rates from the injection site (TD^{2h}) were not significantly different in any group (*Fig. 4*).

DISCUSSION

The most important finding of our study is the observation that subjects who did not develop arm lymphedema or had only mild arm lymphedema had functional lymph nodes within the operated axilla. The origin of these visualized axillary lymph nodes is not clear. It is likely that they were missed during the surgery since complete removal of all axillary nodes is not always possible. Bourgeois (8) observed incomplete axillary node dissection in 35.8% of women in his series and at 1 year follow-up, he observed more frequent development of lymphedema in this group. The possibility of regeneration of regional lymph nodes might be an attractive hypothesis. However, lymph node regeneration in humans remains speculative and requires future study (9-10). Lack of

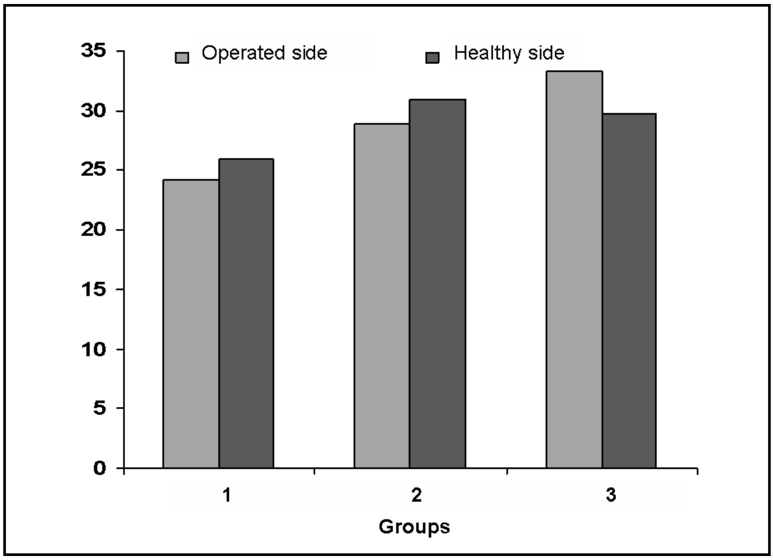

Fig. 4. Tracer disappearance rate from the injection site 2 hours post-injection (%) in all groups. No significant differences were found.

lymph nodes in the group with severe lymphedema may be the result of better surgical axillary clearance and/or effects of radiation therapy.

Enhanced cutaneous lymphatic network, as a result of increased recruitment of dormant lymphatic vessels and/or (presumably) lymphangiogenesis, has been observed in breast cancer-related lymphedema in several studies. An increased number and dilatation of functional vessels might represent a compensatory mechanism, which helps to maintain the ratio of local tissue drainage (6,11-12). It is also suggested that existence of peripheral lymphovenous communications may protect against development of arm lymphedema (13-14).

Postmastectomy lymphedema may be explained as the result of lymphatic (11) and/or lymphovenous communication overload (15). That overload may be due to both excessive interference in the anatomy of the axilla (with only minimal residual lymphatic transport) and hereditary or constitutional anatomical predispositions. Indeed, individual variation in lymphatic/venous function seems to be an important factor in development of breast cancer-related lymphedema (11,14-15).

The correlation between the presence of functional axillary lymph nodes and lack of lymphedema indicates that subjects without arm lymphedema had significantly better lymphatic outflow through the operated axilla than the group with severe lymphedema, possibly due to lesser damage to the axilla during breast cancer treatment.

In our study, the tracer disappearance rate from the injection site was not affected in any studied group. This observation is partially in agreement with other studies, where lymphatic transport from the injection site was reduced in lymphedema affecting the hand or remained unchanged in subjects in whom the hand was spared (6,15) and may indicate the non-specificity of this parameter.

CONCLUSIONS

Women after breast cancer surgery without arm lymphedema or with mild lymphedema have significantly better lymphatic transport through the operated axilla compared to women who developed severe arm lymphedema. However, transport and axillary appearance in all groups was reduced compared to the healthy side.

Presence of functional axillary lymph nodes after axillary surgery may protect against development of postmastectomy arm lymphedema.

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