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PROSPECTIVE EVALUATION OF A PREVENTION PROTOCOL FOR LYMPHEDEMA FOLLOWING SURGERY FOR BREAST CANCER

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ABSTRACT

Lymphedema is a common complication of axillary dissection and thus emphasis should be placed on prevention. Fifty-five women who had breast-conserving surgery or modified radical mastectomy for breast cancer with axillary dissection were randomly assigned to either the preventive protocol (PG) or control group (CG) and assessments were made preoperatively and at 1,3,6,12 and 24 months postoperatively. Arm volume (VOL) was used as measurement of arm lymphedema. Clinically significant lymphedema was confirmed by an increase of at least 200 ml from the preoperative difference between the two arms. The preventive protocol for the PG women included preoperative upper limb lymphscintigraphy (LS), principles for lymphedema risk minimization, and early management of this condition when it was identified. Assessments at 2 years postoperatively were completed for 89% of the 55 women who were randomly assigned to either PG or CG. Of the 49 women with unilateral breast cancer surgery who were measured at 24 months, 10 (21%) were identified with secondary lymphedema using VOL with an incidence of 8% in PG women and 33% in CG women. These prophylactic strategies appear to reduce the development of secondary lymphedema and alter its progression in comparison to the CG women.

Keywords: lymphedema, prevention, breast cancer, axillary dissection, lymphangio-scintigraphy, lymphatic-venous anastomoses

Secondary arm lymphedema is a common and disabling complication of breast cancer treatment. A degree of arm swelling in the early postoperative period may only be a transient reaction to the surgical and radiotherapy treatments and tends to regress spontaneously within a matter of weeks (1-3). Lymphedema may arise at any time, months or years after breast cancer surgery (even over 20 years after the initial treatment) (4-6). However, about 75% of cases occur in the first year after surgery (7-10). Quoted prevalence rates for secondary arm lymphedema vary from 5 to 60% in different studies (11-12), perhaps as a consequence of differences between the number of cases examined, different levels of awareness of the problem, measurement methods, lack of a universal definition of criteria used for the diagnosis of lymphedema, duration of follow-up, and surgical procedures performed. The major risk factors for later development of arm

lymphedema comprise "rough" surgical technique, extent of axillary dissection, axillary radiotherapy, and complications in wound healing including those caused by bacterial infection (13). The surgical procedure on the breast does not appear to influence the incidence of arm lymphedema. Using atraumatic surgical technique, tissues can be minimally injured and resprouting of lymphatics facilitated (14), allowing for new lymphatic-lymphatic or lympho-venous connections. Such lymphangiogenesis and lymphvasculogenesis improves the lymphatic transport capacity (15).

The potential later development of lymph stasis in the upper extremity may be to some extent unavoidable after axillary nodal dissection including sentinel node(s) removal. It is only a matter of time (sometimes years) before a first episode of dermatolymphangio-adenitis or minor trauma occurs, and lymphedema then becomes clinically manifest (13).

The question remains open, however, as to which patients will develop overt lymphedema and which will remain "latent" for lymphedema. This prospective randomized controlled study was designed to objectively determine the effects of a specific protocol of prophylactic measures on the development of secondary lymphedema and to assess the role of early lymphscintigraphy in evaluating the extent of lymph stasis and in predicting the likelihood of later development of arm lymphedema.

PATIENTS AND METHODS

Patients scheduled to undergo breast-conserving surgery or modified radical mastectomy for breast cancer were randomly allocated to either the PG or CG group. All patients signed an informed consent and the study was approved by the Institutional Review Board. The study included a total of 55 patients (mean age 54.07; SD=10.54) who underwent either breast-conserving surgery (12 patients in the PG group and 13 in the CG group) or modified radical mastectomy (13 patients in the PG group and 11 in the CG group) depending on the stage of the breast cancer. All had complete axillary dissection (AD) either because they were not candidates for sentinel lymph node biopsy (clinical N1 or N2 disease – 34 patients) or had a positive sentinel node requiring secondary AD (21 patients).

All patients received radiotherapy and there was little difference between the two groups in the sites that were irradiated with the breast being the most common site, then the chest wall, supraclavicular fossa and internal mammary chain in decreasing frequency.

Exclusion criteria included four patients where the planned axillary dissection was not performed and 18 women who either declined lymphscintigraphy preoperatively or who had difficulty following the protocol guidelines.

Each woman was assessed preoperatively and then postoperatively at 1, 3, 6, 12, and 24 months.

Arm volumes (VOL) were assessed using water displacement and measured to the nearest 5 ml. The difference between the VOL measurements of both arms (operated arm=OA; unoperated arm=UOA) was determined. Both arms were measured at each review period and compared to preoperative data. The use of the difference between the two arms ensured that changes measured in the operated arm (that may have indicated early lymphedema) were not due to variability in arm volume over time. The criteria used to identify early secondary lymphedema included a difference of over 200 ml from preoperative VOL measurements (OA – UOA VOL) (16-17), which has found to be clinically detectable as edema.

The preventive protocol for the PG women (25) included preoperative upper limb lymphscintigraphy (LS) (18-20), principles for lymphedema risk minimization (21), and early management of this condition when it was identified (22). LS was performed pre-operatively and 6 months after breast cancer surgery only in the PG group to display
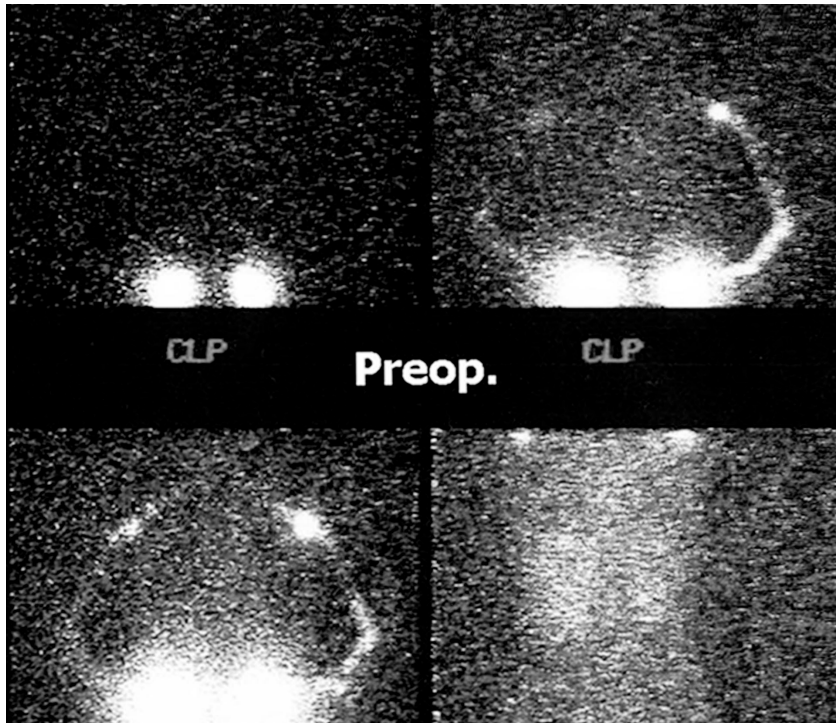
Fig. 1: Pre-operative lymphscintigram displays lymphatic impairment (delayed/reduced earlier tracer transport and lower tracer accumulation in axillary nodes on the later image) in the right arm in a PG patient scheduled for treatment of a right breast cancer. See Fig. 3 for comparison.

different lymphatic patterns, including no demonstrable lymph drainage with marked tracer dispersion (dermal back flow) throughout the arm (severe lymphatic impairment – LI), partially intact lymphatic collectors but with tracer dispersion in the forearm (mild to moderate LI), intact trunks without dermal back flow (no LI).

In 18 women with negative LS (NEG LS), the preventive protocol included the use of blue dye (Blue Patent V) injected at the volar surface of the arm at the time of breast cancer surgery in order to depict and try to preserve lymphatic vessels. The use of blue dye injection to visualize and protect the outflow lymphatic conduit at the time of node dissection has previously been reported under the label ARM (Axillary Reverse Mapping) procedure (23). The NEG LS group was followed up clinically (VOL) and by lymph-scintigraphy at 6 month post-op.

Seven patients with positive LS (POS LS) underwent a microsurgical operation of lymphatic-venous multiple anastomoses (24) at the volar surface of the proximal third of the arm performed at the same time of axillary nodal dissection (*Figs.1-3*). This procedure has been previously reported (25) to contribute to prevention of arm lymphedema.

When post-op LS pointed out disruption or blockage of arm lymphatic drainage before the onset of limb swelling, women in the PG group underwent early use of elastic sleeves, supplemented by manual lymphatic drainage, prophylactic external compression, and remedial exercises (26).

In case of appearance or worsening of lymphedema notwithstanding the physical methods, the patients underwent early microsurgical operation (27,28).

In the CG women, once a volume abnormality was determined, the standardized
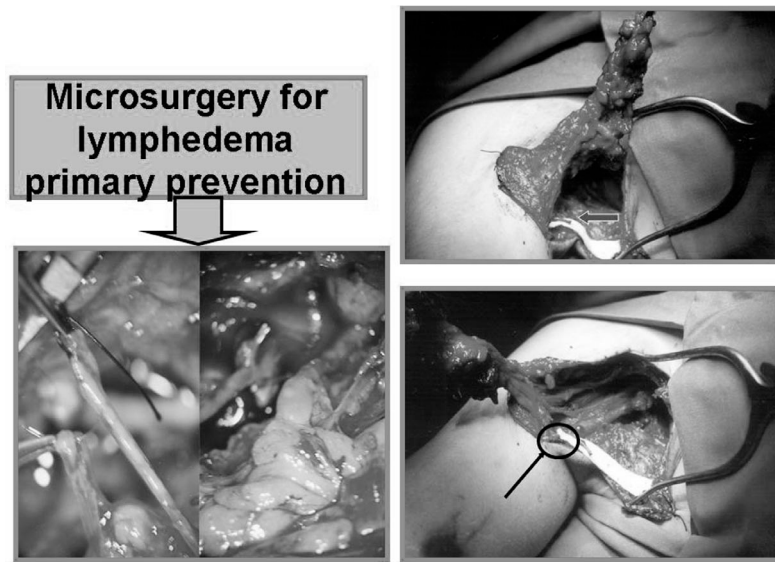
Fig. 2: Treatment of the patient in Fig. 1 included completing axillary lymph nodal dissection with lymphatic-venous microanastomoses (LVA, lower left) performed at the superior third of the volar surface of the arm (right side). Lymphatic vessels draining the arm are visualized by the blue dye injected at the forearm.
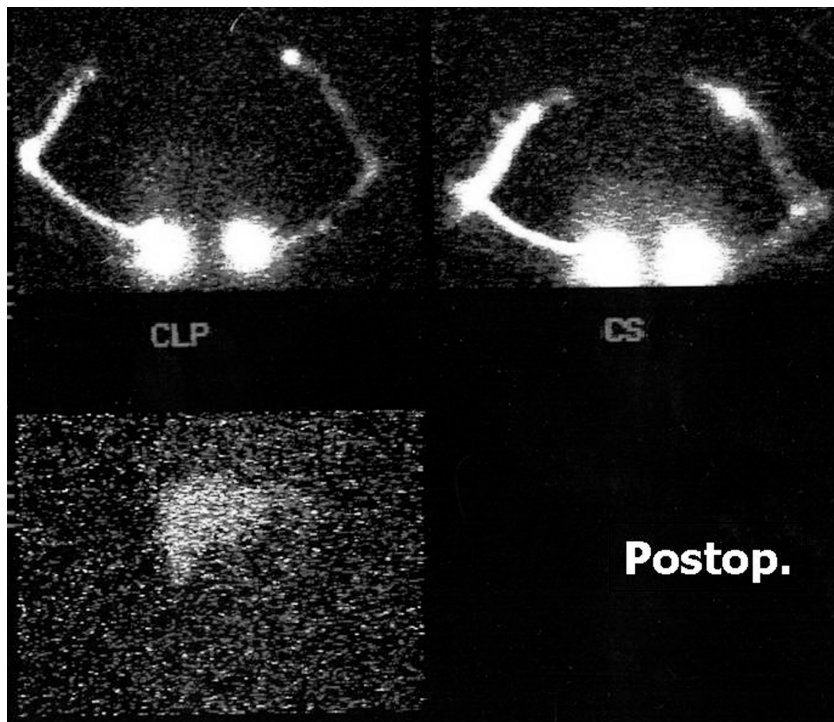

Fig. 3: Lymphscintigram followup in the same PG patient displayed in Figs. 1 and 2 showing the marked improvement of lymphatic drainage in the right arm (prompt early tracer transport and increased tracer accumulation to point of anastomosis) following the microsurgical lymphatic-venous shunt at the time of the axillary dissection.

diagnostic (including LS to document lymphatic insufficiency) and therapeutic procedures to assess and non- operatively treat lymphedema were carried out.

Statistical analysis

The comparison between scale variables age, BMI, lymph nodes removed, metastatic lymph nodes (MLN), surgical procedure, axillary dissection level, site of radiotherapy, wound infection, operated arm (OA) volume at baseline in PG and CG was performed using t-test as data were normally distributed (one-sample Kolmogorov-Smirnov p-value NS for every variables). As variable "MLN" was not normally distributed both in PG (one-sample Kolmogorov-Smirnov p-value = 0.004) and CG (p-value = 0.003), Mann Whitney-test was used. Nominal baseline variables were compared using Chi square or Fischer's Exact Test.

The comparison between percentage increase in comparison with baseline volume after 1, 3, 6, 12, and 24 months from operation in PG and CG was performed using the Mann Whitney test (between groups) and Wilcoxon test (between timing), as data were not symmetrically distributed and normal distribution could not be assumed as demonstrated using one-sample Kolmogorov-Smirnov test (see Results section). The percentage increase was represented by box plots showing the median, inter-quartile range, outliers and extreme cases of variables. Number of patients with increase >10% at different timing in PG and CG were compared using 2-sided Fischer's Exact Test.

RESULTS

Assessments at 2 years postoperatively were completed for 89% (49) of the 55 women who were randomly assigned to either PG (25) or CG (24).

Of the 49 women with unilateral breast cancer surgery who were measured at 24 mo., 10 (21%) were identified with secondary

lymphedema using VOL (OA-UOA). The PG women had an incidence of 8% (2) and the CG women had an incidence of 33% (8). Clinically significant secondary lymphedema was confirmed in 100% of cases by an increase of over 200 ml in the VOL at 24 mo. The frequency of lymphedema appeared to be higher in women who had breast-conservation surgery than in those who had a mastectomy. Our team of surgeons were involved in the operations, but this did not affect the outcome as the appearance of arm lymphedema did not depend on the surgical technique. We find that the appearance of lymphedema is mainly linked to the number of lymph nodes removed and the patient's congenital predis-position more than the surgical technique. Differences in radiation dosages and sites of radiation between the PG and the CG were not significant (see *Table 1*).

Data Analysis

Demographic and surgical data and OA baseline volumes are reported in *Table 1*. No significant differences were observed regarding age, BMI, lymph nodes removed, MLN, surgical procedure, axillary dissection level, site of radiotherapy, wound infection, and operated arm (OA) volume.

The baseline volumes in PG and CG were overlapping both in terms of central trend index (mean and median) and absolute dispersion (standard deviation and range). The percentage increases in comparison with baseline volume after 1, 3, 6, 12 and 24 months in PG and CG are reported in *Table 2*. The data distribution is not normal for PG at 3 months (one-sample Kolmorov-Smirnov test p-value=0.001) and 6 months (p-value = 0.001) and for CG at 3 months (p-value < 0.001), 6 (p-value = 0.003), 12 (p-value = 0.008) and 24 (p-value = 0.011) months.

PG and CG showed similar percentage increase at 1 month (Mann Whitney test p-value = 0.873) and 3 month (p-value = 0.734). The increase of volume was higher in the Control Group in comparison with PG at 12

TABLE 1
The Study Population

	New Protocol	Control	p-value
Subjects (n)	25	24	
Age (yrs) (mean±SD)	53.4±7.2	54.6±7.9	NS
BMI (Kg/m^2) (mean±SD)	27.3±5.4	29.9±6.8	NS
Lymph nodes removed (mean±SD)	15.2±3.8	15.1±3.8	NS
MLN (n) (mean±SD)	1.5±1.8	1.4±1.7	NS
Surgical Procedure (n)			
CLE & AD	12	13	
MRM & AD	13	11	NS
Axillary dissection level			
I	4	5	
II	17	13	
III	4	5	NS
Radiotherapy (n)			
Breast	15	14	
Chest wall	4	3	
Internal mammary chain	3	2	
Supraclavicular fossa	3	3	NS
Wound infection (n)	3	3	NS
OA Baseline Volume (ml)			
mean±SD	2,144±618	2,163±623	NS
95% Confidence Interval	1,889-2,400	1,901-2,427	
Median	2,140	2,143	
Min-Max	1,235-3,100	1,235-3,100	

AD= Axillary Dissection; CLE=Complete Local Excision; MLN=Metastatic Lymph Nodes; MRM=Modified Radical Mastectomy; OA=Operated Arm

month (p-value=0.038) and 24 month (p-value = 0.012), while at 6 month the difference was not statistically significant (p-value = 0.17). The number of patients with a volume increase >10% is shown in *Table 2*, and the proportion was higher in the CG at 12 month (Fischer's Exact Test p-value = 0.004) and 24 month (p-value=0.004) (*Fig. 4*).

DISCUSSION AND CONCLUSIONS

The overall incidence of clinically evident secondary lymphedema at 2 years after unilateral breast cancer surgery was 21% in this study. All women were at risk of developing secondary lymphedema due to the surgical excision of the axillary lymph nodes. The clinical changes in the operated arm were confirmed by an increase of at least 200 ml from the pre-operative volumetric measurements. At 2 years, 33% of the CG women had been identified with secondary lymphedema compared to only 8% of the PG women.

Most of the CG women detected with an increase of 200 ml from their pre-operative volumetry had persistent changes in arm volume from 6 to 12 months postoperatively.

TABLE 2
Percentage Increase in Arm Volume Compared with Baseline Volume

	Time after operation (months)				
	1	**3**	**6**	**12**	**24**
Prevention Group (n=25)					
Mean±SD	3.8±1.7	0.9±1.6	2.4±4	1.1±0.6	1.3±0.7
95% Confidence Interval	3.1-4.5	0.3-1.6	0.7-4	0.9-1.4	1.0-1.6
Median	3.5	0.5	1.2	1.2	1.1
N (%)>10	0	0	2 (8)	0	0
Wilcoxon p-value (in comparison with the previous time period)		<0.001	<0.001	0.036	0.022
Control Group (n=24)					
Mean±SD	3.7±1.7	2.8±6.3	6.2±8.6	7.8±9.8	8.3±10.1
95% Confidence Interval	3.0-4.4	0.2-5.5	2.6-9.9	3.7-11.9	4.0-12.5
Median	3.4	0.5	1.4	1.7	1.9
N (%)>10	0	2 (8.3)	6 (25)	8 (33.3)	8 (33.3)
Wilcoxon p-value (in comparison with the previous time period)		0.028	<0.001	<0.001	<0.001

For two PG women, secondary lymphedema was first detected at 24 months but there tended to be a steady progression in the difference between the OA and UOA. In comparison, the pattern of change in volume measurements was inconsistent for the surviving women in the PG or CG, and in the majority of cases, did not exceed the clinical criteria. There were several CG women who had increases in arm volume but at the time of their 2 years review did not have clinically significant lymphedema.

Using the volumetric criteria and clinical signs, this study has demonstrated that the incidence of early secondary lymphedema at 24 months is similar to that detected previously in women who were assessed at later stages postoperatively when the only postoperative difference between the arms was considered. In the majority of women, changes consistent with lymphedema were detected from 6 months postoperatively suggesting the early onset of significant

secondary lymphedema may be detected with clinical assessment and objective measurement within the first year postoperatively. The early detection may result in more effective management and the resolution of acute/subacute lymphedema before it develops into a more chronic condition, identifying as a high priority the early detection and possible benefits of early intervention for secondary lymphedema (21).

Secondary arm lymphedema has been identified in 21% of the women who were assessed at 2 years after unilateral breast cancer surgery using a comparison to the preoperative measurements for each woman. The criterion, an increase of >200 ml from the preoperative volumetric conditions, was determined to be a sensitive measurement to detect early clinically significant secondary lymphedema.

The qualitative results of this study suggest that the strategies incorporated into the preventive protocol for prevention as well
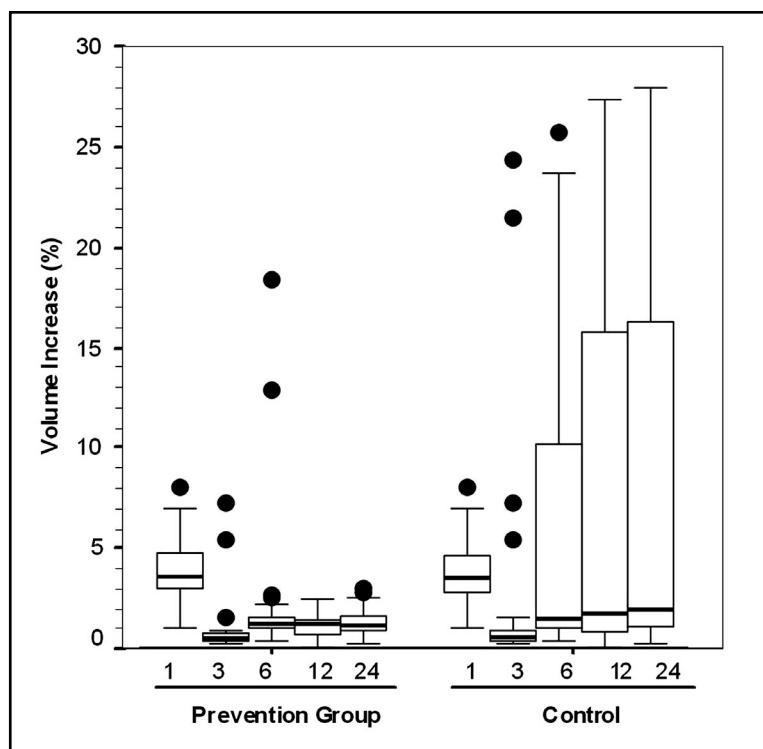
Fig. 4: Percentage increase in arm volume is represented by box plots showing the median, inter-quartile range, outliers and extreme cases of variables. Number of patients with increase >10% at different timing in Preventive Protocol and Control groups were compared using 2-sided Fischer's Exact Test. Median for each dataset is indicated by the black center line, and the first and third quartiles are the edges of the box area (inter-quartile range, IQR). The extreme values (within 1.5 times the inter-quartile range from the upper or lower quartile) are the ends of the lines extending from the IQR. Points at a greater distance from the median than 1.5 times the IQR are plotted individually as circles. These points represent potential outliers.

as early intervention of secondary lymphedema do influence the occurrence and severity of secondary lymphedema in the PG women compared to those in CG. At 24 months after breast cancer surgery, the CG women had four times the incidence of secondary lymphedema compared to the PG, and in two-thirds of the CG women it was detected at 6 months postoperatively. The extension of this study to monitor the progress of the surviving women for an additional 3 years postoperatively is ongoing to provide further information on these early effects on the incidence and progression of secondary lymphedema after breast cancer surgery due to the use of this diagnostic and therapeutic preventive protocol.

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