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CLINICAL TRIAL

A randomized control study of treating secondary stage II breast cancer-related lymphoedema with free lymph node transfer

Dimitrios Dionyssiou[1] · Efterpi Demiri[1] · Antonis Tsimponis[1] · Alexandros Sarafis[1] · Vasillios Mpalaris[1] · Georgia Tatsidou[1] · Georgios Arsos[1]

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Abstract Microsurgical techniques are increasingly used for treating severe lymphoedema cases. The purpose of this study was to evaluate the effectiveness of free vascularized lymph node transfer (LNT) in stage II breast cancer-related lymphoedema patients in comparison with non-surgical management. During the last 3 years, 83 female patients were examined at our lymphoedema clinic. Finally, 36 cases were included in this study and randomly divided in two groups: group A patients ($n = 18$, mean age 47 years) underwent microsurgical LNT; followed by 6 months of physiotherapy and compression, while group B patients ($n = 18$, mean age 49 years) were managed by physiotherapy and compression alone for 6 months. Patients of both groups removed their elastic garments after 6 months and were re-examined 1 year later. All the 36 patients had detailed evaluation of the affected extremity including limb volume measurement, infection episodes and scale scoring of pain, feeling of heaviness and functional status both at baseline and 18 month. Limb volume reduction was observed in both groups; mean reduction was greater in group A (57 %) than in group B (18 %). Infection episodes in group A were significantly reduced compared to those in group B patients. All group A patients reported painless and feeling of heaviness-free extremities with overall functional improvement, while the corresponding changes in group B patients were no more than marginal. Moreover, the LNT procedure was estimated as cost effective compared to conservative treatment alone. LNT represents an effective therapeutic approach for stage II lymphoedema patients; it significantly reduces limb volume, decreases recurrent infections and improves the overall function.

Keywords Lymph node transfer · Lymphoedema treatment · Physiotherapy

Introduction

Symptomatic lymphoedema is frequently associated to severe morbidity, including pain and feeling of heaviness of the affected limb, disability on the daily activities and serious aesthetic concerns. Moreover, lymphoedema patients are prone to develop recurrent infection episodes, which may present as cellulitis, erysipelas or lymphangitis, requiring oral antibiotic treatment and, quite frequently, long hospitalization for intravenous antibiotic therapy [1, 2]. The psychosocial impact of lymphoedema in breast cancer-related lymphoedema (BCRL) patients has been described to be as distressing, as the initial diagnosis of breast cancer [2].

Management of lymphoedema traditionally consisted of conservative treatments, including manual lymphatic drainage, compression garments, pneumatic pumps and multilayer bandaging. Recently, microsurgical procedures, namely vascularized lymph node transfers [3], lymphaticovenous anastomoses [4, 5], lymphatic-venous-lymphatic plasties [6] and lymphaticolymphatic grafts [7] are being used in an increased fashion and considered to offer an effective treatment to severe lymphoedema cases [2].

Corinne Becker has pioneered the introduction of vascularized lymph node flap and described the lymph node transfer (LNT) technique as a logical reconstructive approach of the lymphoedema sequelae; the flap bridges the injured and interrupted lymphatic pathways and re-

✉ Dimitrios Dionyssiou
ddionyssiou@gmail.com

[1] Aristotle University of Thessaloniki, Thessaloniki, Greece

establishes the lymphatic flow by promoting lymphangiogenesis [8]. Saaristo et al. studied the mechanism of lymphangiogenesis following LNT and advocated that the vascularized lymph nodes promote the procedure by activating growth factors, such as VEGF-C [9]. The long-term advantages of this microsurgical approach include permanent limb volume reduction, decreased number of infection episodes and total improvement in the patients' quality of life [8].

The aim of this randomized prospective control study is to evaluate the effectiveness of the vascularized lymph node transfer followed by physiotherapy, in comparison with conservative treatment alone, in the management of stage II BCRL patients.

Materials and methods

A randomized control study was designed to evaluate the effectiveness of free vascularized lymph node transfer in stage II breast cancer-related lymphoedema patients in comparison with conservative management. Treatment was offered to both groups for 6 months. Afterwards pressure garments were removed from all patients and they remained with no additional treatment for 12 more months, till their final evaluation.

During a period of 3 years (December 2011–2014), 83 female patients with upper limb lymphoedema related to breast cancer treatment were examined at the outpatient lymphoedema clinic of Papageorgiou Hospital of Thessaloniki by two independent doctors. Diagnosis of lymphoedema was based on clinical examination and confirmed by Tc-99 m-nanocolloid lymphoscintigraphy and non-contrast magnetic resonance (MR) lymphography.

Eligible patients were all women aged 18 or over, suffering from breast cancer and stage II unilateral upper limb lymphoedema, according to the Staging System of the International Society of Lymphology, and at least one infection episode during the last year. Patients with bilateral upper limb lymphoedema, history of bilateral breast cancer, metastatic disease, history of primary lymphoedema, or patients unable to comply with the proposed treatment, were excluded from the study. The study protocol was registered and approved by the hospital's ethics committee and a signed consent form was obtained from all the patients who participated in the study.

According to bibliographic sources, 12 % of women are expected to suffer from breast cancer [10], while around 16.6 % of them were found to be complicated with upper limb lymphoedema [11]. In the given geographical area covered by our hospital, the sample size of our study constitutes 2 % of the general population expected to suffer from this entity.

Thirty-six patients fulfilled the criteria and were assigned the following simple randomization procedures (random number generator) to one of the two treatment groups: group A patients ($n = 18$) underwent vascularized lymph node transfer followed by a postoperative physiotherapy regime for 6 months, while group B patients ($n = 18$) were treated conservatively with the physiotherapy regime without any surgical intervention for 6 months. Treatment was offered to both groups for 6 months; afterwards no further treatment was given to the patients for twelve more months, till their final follow-up. All the patients were examined thoroughly before their allocation into a group. In order to quantify the magnitude of the lymphoedema of the affected limb, the volumes of both the affected and the contralateral healthy limbs were estimated using the truncated cone formula based on 4-cm intervals serial perimeter measurements [12]. Their difference representing the excess volume of the affected limb was expressed as percentage of the volume of the intact limb (EV %). We also recorded episodes of infection, such as erysipelas, cellulitis or lymphangitis, and subjective information, i.e. pain, feeling of heaviness and functional disturbances in a visual analogue scaling system (1–10). Both Group A and group B patients were re-evaluated 18 months after the initial treatment (Table 1).

Patients in group A had a mean age of 47.7 years (ranged from 32 to 77) and a mean BMI of 28.2, while in group B the mean age was 49.1 (ranged from 30 to 71) and the mean BMI was 27.7.

In group A patients, the lymph node flaps were raised from the lower abdominal and upper groin area based on the superficial inferior epigastric artery ($n = 8$) and the superficial circumflex iliac artery ($n = 10$). The selected lymph nodes were all situated above the inguinal crease. The flaps included 1–3 lymph nodes and their mean size was 5.5 × 3.8 cm (length 4–7 cm and height 3–4.5 cm). All flaps were raised sharply with scalpel and/or scissors, avoiding the use of diathermy, while liga-clips were mostly applied at the donor area for hemostasis, in order to reduce the risk of seroma or haematoma. The flaps' pedicle was anastomosed at the axillary region with branches of the thoracodorsal or posterior circumflex vessels in an end-to-end fashion after aggressive removal of all scar tissue. The lymph node flaps contained adipose tissue without any skin paddle, and were placed and secured with sutures at the area where the lymphatic vessels at the upper arm were obstructed, based on the findings of the preoperative MRI investigation. The donor site was closed primarily in all cases after placing a No. 12 suction drain.

The proposed physiotherapy protocol for both groups included manual lymphatic drainage (MLD) for the first month (daily for two weeks and twice per week for the following two weeks) and pressure garments (class II,

Table 1 The baseline demographic, somatometric and clinical data of the patients of both groups A and B

Group A	V % pre	V % post	I pre	I post	P pre	P post	H pre	H post	F pre	F post
1	21	8	1	0	6	0	9	0	5	1
2	63	24	2	0	10	1	10	0	8	1
3	37	19	1	1	7	1	10	2	7	2
4	22	9	2	0	4	0	3	0	2	0
5	16	6	1	0	2	0	2	0	2	0
6	35	17	1	0	4	1	5	0	5	1
7	53	27	1	0	5	1	5	1	5	0
8	47	20	2	1	6	1	6	0	5	2
9	51	18	7	0	7	1	9	3	9	3
10	28	8	2	0	5	2	7	2	9	2
11	33	14	2	0	6	0	8	4	8	3
12	38	21	1	1	5	0	5	0	2	0
13	57	18	3	1	4	0	4	0	7	1
14	18	7	2	0	3	1	2	0	3	0
15	26	13	1	0	5	0	5	0	2	0
16	36	9	1	0	6	1	10	3	8	3
17	45	27	4	1	5	0	5	0	4	1
18	33	18	1	0	7	1	9	2	8	2
Mean	36.61	15.72	1.94	0.277	5.38	0.61	6.33	0.94	5.5	1.22
Group B	V % pre	V % post	I pre	I post	P pre	P post	H pre	H post	F pre	F post
1	33	24	1	0	5	3	7	3	5	2
2	47	42	3	2	7	7	9	9	8	9
3	29	30	1	2	7	9	9	10	6	8
4	45	34	2	2	8	5	7	3	1	0
5	34	25	1	1	5	4	9	4	1	0
6	20	17	1	0	3	3	3	3	4	4
7	38	29	1	0	5	3	5	5	4	3
8	21	14	2	1	4	2	8	4	3	1
9	19	17	1	1	3	3	2	3	9	9
10	34	19	1	0	5	4	5	3	9	5
11	57	59	4	3	8	9	10	10	8	10
12	22	13	1	0	2	2	3	0	2	1
13	54	40	2	1	6	5	5	5	7	7
14	37	25	1	1	4	3	4	4	3	2
15	39	30	2	1	3	2	4	4	2	1
16	62	50	2	2	9	7	10	6	8	6
17	53	51	1	1	6	6	8	9	4	6
18	31	34	2	3	4	6	4	7	8	9
Mean	37.5	30.72	1.61	1.16	5.22	4.61	6.22	5.11	5.11	4.61

V volume (% difference of oedema); *I* infection (episodes per year per patient); *P* pain; *H* heaviness; *F* function; (P, H, F scale 0–10); *P 0* less pain; *10* the worst pain; *H 0* less heaviness; *10* worst heavy sensation; *F 0* no functional problem, *10* no function

30 mm Hg, pressure sleeves worn day and night) for the next 5 months. The operated patients were also educated to apply gentle pumping pressure onto the flap for emptying the excess fluids 4 × 10 times daily for the first 3 months. All patients were discontinued of any conservative management for the following 12 months.

Group A patients underwent a postoperative lymphoscintigraphy, 6 months after the microsurgical

procedure, in order to evaluate the viability and functionality of the transferred lymph nodes.

Our study was completed by calculating and comparing the costs of treatments applied in each group, i.e. the cost of surgical treatment plus physiotherapy in group A patients and the potential cost of the lifelong conservative management in group B patients. More specifically, estimating the overall costs for group A patients, we recorded and analysed the expenses of the operation, medication, hospital stay, relevant imaging and biochemical tests, physiotherapies and pressure garments, according to our National Social Security costing system; for group B patients, after estimating life expectancy in Greece, according to the updated WHO data, the costs of physiotherapy sessions and pressure garments, for the expected rest of their life, were also calculated [13].

Statistical analysis

Statistical analysis was performed using the SPSS v 17.0 statistical software. Normality assumption for continuous variables was checked using the Shapiro–Wilk test. Mann–Whitney U and Student's *t* test were used to compare the results of each treatment, while paired *t* test and Wilcoxon Signed-Rank test were applied to check the effectiveness of both therapies regarding the various parameters, i.e. volume reduction, pain, heaviness, infection rate and overall function of the affected upper extremity of both groups. Statistical significance was accepted at p values less than 0.05.

Results

The baseline demographic, somatometric and clinical data of the patients in both groups A and B are summarized in Table 1, confirming successful randomization with no dissimilarities between the two groups.

All patients conformed well to the offered treatment. In group A, the postoperative course of the LNT procedure was uneventful; major complications, i.e. wound dehiscence, infection or lymphoedema at the donor area, were not observed. Two patients reported a mild discomfort at the donor side lower limb, which subsided within two weeks after the operation. Two more patients of the group A had a prolonged lymphorrhea at the donor area, which was managed by keeping the drains in place for 14 and 20 days, respectively. Postoperative lymphoscintigraphy of the group A patients showed functional activity of the implanted lymph nodes in 13 out of 18 patients (72 %).

The values concerning the volume of the affected limbs, the infection rates, the feeling of pain and heaviness and the overall function were measured at the induction of patients in the study and 18 months afterwards (6 months of treatment plus 12 months of regular activities with no treatment), and are presented in Table 2.

The volume of the affected limb was significantly decreased ($p = 0.000$, Table 2) after treatment in both groups. The mean volume reduction was significantly higher in group A compared to group B patients (57 % versus 18 %, $p = 0.000$, Table 3), indicating superior post-treatment results in group A.

Regarding the infection episodes, the mean number of episodes per patient per year for the last year before treatment were 1.94 and 1.61 in group A and group B, respectively. At the final follow-up, a mean of 0.27 infection episodes per patient in group A and 1.16 in group B were recorded. The evaluation of each treatment showed a significant reduction of infection rate in both groups ($p = 0.000$ in group A and $p = 0.016$ in group B) as shown in Table 2. Comparing the results of the two therapeutic modalities, surgical treatment followed by physiotherapy was proven significantly more effective ($p = 0.001$) compared to the conservative treatment alone (Table 3).

As for the subjective symptoms, all group A patients reported significant reduction of pain ($p = 0.000$) and feeling of heaviness ($p = 0.000$) of the affected extremity with significant overall functional improvement ($p = 0.000$) (Table 2). In group B, ten patients reported reduction of

Table 2 Correlation of mean volume reduction, pain, heaviness, infection rate and overall function of the affected upper extremity in both groups A and B before and 12 months after the completion of any treatment

Group	Mean volume pre	Mean volume post	*p*
A	36.61	15.72	0.000
B	37.5	30.72	0.000
	Mean infection rate pre	Mean infection rate post	*p*
A	1.94	0.277	0.000
B	1.61	1.16	0.016
	Mean pain scale score pre	Mean pain scale score post	*p*
A	5.38	0.61	0.000
B	5.22	4.61	0.077
	Mean heaviness scale score pre	Mean heaviness scale score post	*p*
A	6.33	0.94	0.000
B	6.22	5.11	0.058
	Mean functional score pre	Mean functional score post	*p*
A	5.5	1.22	0.000
B	5.11	4.61	0.226

Table 3 Differences in the affected upper extremity volume, infection rate, feeling of pain, heaviness and overall function in group A and group B patients

Differences	*A*	*B*	*p*
Mean difference in volume	20.88	6.77	0.000
Mean difference in infection rate	1.66	0.44	0.001
Mean difference in pain scale score	4.77	0.61	0.000
Mean difference in heaviness scale score	5.38	1.11	0.000
Mean difference in overall function score	4.27	0.5	0.000

pain, while seven patients reported reduction of heaviness; only ten patients stated subjective functional improvement of the involved limb, while eight reported no functional changes. All of the three subjective variables (pain, heaviness, function) showed only limited improvement after conservative treatment alone in group B, not reaching statistical significance ($p = 0.077$, $p = 0.058$, $p = 0.226$ respectively, Table 2). For all of the above-mentioned three parameters, the conservative treatment alone was proven clearly inferior compared to the surgical treatment applied to group A patients ($p = 0.000$ for all, Table 3).

The mean overall cost per patient in group A, including the hospitalization period, relevant imaging and biochemical tests and the operation, twenty sessions of physiotherapy and the cost of the bandages and pressure garments which were used, was estimated as high as 6465 euro. For group B patients (mean age 49.1 years), assuming that life expectancy in Greece is 84 years based on the WHO data published in 2013 [11], the estimated mean overall cost of this lifelong conservative management, with a mean 10 sessions of physiotherapy per year and change of pressure garments every 6 months for the remaining 34.9 years of the patient's life, is raised up to 26,175 euro.

Moreover, hypothesizing a twice per year antibiotic therapy need and hospital stay for treating recurrent infection episodes, the mean additional cost might increase by an extra amount of 119,944 euro per each group B patient. In those expenses, but also of importance, the cost of the paid sick leave days, the absence of the work and, of course, the family social impact are not included.

Discussion

Conservative management of upper limb BCRL is based on the complex decongestive physiotherapy (CDT), which includes low-stretch bandaging, manual lymphatic drainage, exercises, infection protection and skin care [14]. In the last decade, several studies have reported on the safety and efficacy of the lymph node transfer procedure for the treatment of breast cancer-related lymphoedema [15–17]. However, the literature lacks head-to-head prospective, randomized clinical studies between microsurgical therapies and conservative management.

In our prospective, randomized clinical study, we aimed to compare the short- and long-term outcomes, safety and cost effectiveness in highly selected cohort of patients for the treatment of BCRL. Both group patients followed a homogeneous physiotherapy protocol as per lymphoedema specialized physiotherapists. Our results showed that 1 year after completion of physiotherapy protocol, the patients of group A who underwent the LNT procedure before physiotherapy had a significantly lower recurrence rate of lymphoedema, as compared to those who were managed with physiotherapy alone (group B); almost 80 % of the group B patients returned to their previous lymphoedema situation.

There is a plethora of studies on stage I–III lymphoedema patients who were managed by CDT for a period ranging from 3 days to 6 months. Unfortunately, the majority of these studies lack detailed information on the specific physiotherapy protocol, the kind of bandages or pressure garments, the duration of treatment and elastic sleeve application [14, 18, 19].

Several authors, reporting on the long-term follow-up of physiotherapy-alone managed patients, have published variable rates of lymphoedema recurrence; in a 3-year follow-up study of 177 patients, Foldi et al. have documented that the effect of physiotherapy remained in 54 % of the patients [14]. Others have reported variable outcomes on the volumes of the involved arms, which were stable, increased or decreased [20, 21]. In all these studies, patients were obliged to continuously wear pressure garments, and lymphoedema recurrence depended on the patients' dedication to the proposed conservative treatment.

A serious drawback of managing lymphoedema patients with physiotherapy alone is the need to repeat periodically complex physical therapy and to apply day and night pressure garments, which should be frequently replaced when they become loose or tight, or when lymphoedema recurs [21, 22]. Most published data show that conservative management of BCRL is a non-stop palliative care and failure to comply with the intensive physiotherapy program would finally result in affecting the patients' quality of life [21, 22].

Although patients with upper limb lymphoedema are prone to recurrent infection episodes due to a local immune deficiency, the true incidence of infections is underestimated. Additionally, each episode of cellulitis may further damage the lymphatic system and therefore recurrent infections may lead to the progression of a secondary lymphoedema in a more severe disease [23, 24].

Relevant infection studies have shown the advantages of lymphoedema volume reduction in the occurrence of cellulitis, erysipelas or lymphangitis episodes, while long-term physiotherapy not only promotes the maintenance of limb function, but also affects positively the incidence of recurrent infections [24, 25]. However, women with BCRL are still at risk of lymphoedema recurrence and infection episode even if they reliably adhered to conservative management. In those cases, there is an incurred higher medical cost which suggests that further efforts should be made to elucidate reduction and prevention of BCRL [2].

Granzow et al. in a retrospective study on 26 lymphoedema patients, of which 16 underwent microsurgical lympho-venous anastomoses (LVA) or vascularized LNT, reported a 111 % limb volume reduction, a significant decrease of both compression garment use and need for physiotherapy and a decreased overall rate of cellulitis from 58 % before surgery to 15 % after surgery ($p < 0.0001$) [26]. Similarly, our study has evidenced a significant reduction of infection episodes per year in patients who underwent a vascularized lymph node transfer, compared to those who followed the conservative management alone; although group B patients also achieved some reduction of infection episodes after treatment, they still experienced frequent episodes of cellulitis and erysipelas.

Concerning the quality of life of BCRL patients, this is interwoven with sensation of pain, feeling of heavy limb and functional disabilities. Several studies suggested the benefits of physiotherapy and compression garments in the quality of life (QOL) of lymphoedema patients, preferably in those with short lymphoedema duration; this observation would support the hypothesis that long-standing lymphoedema with tissue fibrosis may not be amenable to compression alone but may respond to gentle massage which would potentially break down scarring [27–30].

In a study by Kim et al., the QOL was necessarily correlated with the reduction in limb volume; having measured the volume reduction and QOL at baseline, 1 and 6 months in BCRL patients being treated with complex decongestive therapy, the authors recorded a significant improvement in QOL scores at 1 and 6 months compared to those at baseline, despite the values of limb volume reduction not showing relevant changes at the same periods [31]. Based on our experience, we believe that the diversity of physiotherapy protocols, the varying severity and duration of lymphoedema, and also the fluctuating patients' compliance in a lifelong physiotherapy management might contribute to the lack of robust satisfactory results.

Comparing surgical to non-surgical management, there are not much data where the impact of lymph node transfer in the BCRL patients' quality of life is evaluated. In a prospective study of Patel et al., the upper limb circumference, function, body appearance, symptoms and mood domains were all found to be significantly improved following a vascularized LNT procedure. These changes were mirrored by improvements in the overall quality of life ($p < 0.01$) [26].

In our study, we objectively estimated limb volumes and infection episodes, and we used a subjective visual analogue scaling system (1–10) to assess and compare the pain, heaviness and functional disturbances, in both the groups of patients. For all the above-mentioned variables, our results strongly support, in an absolute measuring system, the superiority of the LNT procedure compared to physiotherapy management alone. During the study period, the sensation of pain, feeling of heaviness, functionality, limb volume and infection episodes were significantly improved in the LNT-operated patients followed by the physiotherapy program, in contrast with the marginal improvement of the patients who were managed by conservative treatment alone. However, we should characterize the results of this trial as preliminary, since the follow-up period of our study is limited to 18 months; therefore, longer follow-up and re-evaluation of our patients after 2 to 3 years would be mandatory in order to conclude that the LN transfer may provide stable and permanent results.

The final part of our study focused on a theoretical comparative financial validation of the two therapeutic methods, namely the LNT plus physiotherapy versus the physiotherapy alone schemes. After the long-term calculation of both methods' expenses, we were able to estimate that the microsurgical intervention may represent a significant benefit for the Health system than lifelong conservative management in patients with BCRL. The above observation was based on our LNT series in which no severe complications had been documented; if postoperative complications occur or the LNT procedure does not provide the expected results, the final cost in the operated group of patients should certainly be reconsidered.

Study limitations

Although prospective and randomized, our study suffers a few drawbacks such as the limited number of participants and the rather short follow-up period.

The small number of patients (18 per treatment group) is partly counterbalanced by the careful selection, the successful randomization (Table 1) and finally by the strength of the statistical analysis.

The 18 months' follow-up period may comprise a second issue, but we assume that the encouraging preliminary results of the surgical approach will show long-term stability if not permanence, which of course remains to be

proven. For such a confirmation, studies with considerably lengthier follow-up periods would be appreciated.

Conclusion

Lymph node transfer represents a remarkable therapeutic option for stage II lymphoedema patients; it may significantly increase the functional and aesthetic outcome, decrease the lymphangitis and skin infection episodes and also reduce the need of prolonged hospitalization. For the study period, we have shown that in stage II BCRL patients, the microsurgical lymph node transfer followed by a short physiotherapy program provides an effective treatment superior to physiotherapy alone. After reinforcement by long-term stability evidence, it could be seriously considered as the optimum therapeutic option by the advisory panels.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest and the study was not supported by any pharmaceutical company.

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