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Postmastectomy upper limb lymphedema: Combined vascularized lymph node transfer and scar release with fat graft expedites surgical and patients' related outcomes. A retrospective comparative study

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KEYWORDS
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Summary *Introduction:* Lymphedema resulting from breast cancer treatment is a chronic condition that can significantly compromise quality of life. Several works have documented the efficacy of vascularized lymph node flap transfer (VLNT) for the treatment of advanced-stage lymphedema. Given that the axillary scar may contribute to the patient's existing lymphedema, the authors assumed that combining VLNT and scar release with fat graft could be an effective strategy of treatment. The purpose of this study is to compare the efficacy in the reduction of limb circumference and health-related quality of life between a combined strategy, namely, VLN transfer (VLNT) and axillary scar release with fat grafting, and only VLNT for patients affected by postmastectomy upper limb lymphedema. The idea.
Materials and methods: All patients with stage II and III breast cancer-related lymphedema operated between January 2012 and January 2016 were retrospectively identified, and only those treated by combined VLNT and scar release (Group A) or only VLNT (Group B) were included. The outcomes were assessed clinically by limb circumference measurement and radiologically by lymphoscintigraphy. Lymphedema-related quality of life was evaluated preoperatively and at 1 year follow-up through the LYMQOL questionnaire.

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Results: Thirty-nine patients met inclusion criteria (Group A = 18; Group B = 21). Mean follow-up was 29 months for Group A and 32 months for Group B. Flap survival rate was 100%, with no donor site morbidity in all patients. A statistically significant difference between the circumference reduction rates (RR) at above elbow level was observed at 3 and 6 months of follow-up comparing the two groups ($p<0.00001$), with higher values in Group A than in Group B. No significant difference was detected comparing RR values at above and below elbow at 12 and 24 months postoperatively. LYMQOL metrics showed significantly better scores ($p<0.0001$) in all domains at all follow-up appointments in Group A.
Conclusions: Patients with postmastectomy upper limb lymphedema can benefit from combined lymph node transfer and axillary scar release with fat graft, as this approach seems to fasten the onset of improvement and to have a positive impact on patients' quality of life.

Introduction

Lymphedema is a progressive disease of the lymphatic system characterized by chronic inflammation, adipose deposition, hyperkeratosis, and fibrosis. In the United States and Europe, the most common cause of lymphedema is cancer treatment. Breast cancer survivors comprise the largest group of affected individuals owing to the high incidence of breast cancer in these regions.[1-3] Additionally, lymphedema can occur as a complication of treatment of most other solid tumors, melanoma, pelvic tumors, gynecological cancers, and sarcomas.[4-6]

According to most of the studies published in the current literature, the cumulative incidence of breast cancer-related upper limb lymphedema in a 5-year follow-up period ranges from 3% to 42.2% depending on the assessment of the outcome and characteristics of the sample.[5,7-16] Considering a 10-year median follow-up, an incidence of 29% of lymphedema, as a self-reported outcome, was found among US multiethnic patients who had undergone breast cancer treatment.[15]

The lymphedema may present with the following symptoms: volume increase in the limb; change in skin mechanical properties; sensitivity changes; predisposal to systemic and local infections; development of secondary malignant diseases; stiffness and decrease in the movement amplitude and, consequently, functional decrease of the involved upper limb. In addition to these physical symptoms, the patient may also present lowering of self-esteem and problems with body image and social acceptability.

From conservative therapies to operations performed in severe and refractory cases, treatment of lymphedema remains a challenge.[17-19] Conservative therapy is the backbone for providing symptomatic improvement of lymphedema and slowing down the progression of the disease, but it never results in a cure. Resistance of lymphedemas to conservative therapy, pain or signs of brachial plexus neuropathy, and chronic infection are the preferred indications for autologous lymph node transfer. Several works have documented the efficacy of vascularized lymph node flap transfer (VLNT) for the treatment of advanced-stage lymphedema, including postmastectomy upper limb lymphedema. This method of reconstruction uses common microsurgical techniques to transfer lymph nodes to either the axilla or distally in the arm/forearm to restore lymphatic flow.[20] Different donor sites have been described to be harvested as VLN flaps, including groin, submental, supraclavicular, and abdominal regions.[21-27] The efficacy of the procedure can be evaluated after 1 year because this is period for observing the growth of lymphatics.

In earlier literature,[28] most of the lymph flaps were transferred to the postmastectomy upper extremity, with the flaps placed in the axillary area, as the procedure allowed the excision of the axillary scar and the proximal site provided sufficient soft tissue for primary closure. However, Cheng et al.[29] compared different recipient sites for flap transfer and associated the most distal recipient sites with better results. Hence, effectively, the axillary scar may contribute to a patient's existing lymphedema by obstructing lymph flow and interfering with lymphangiogenesis.

Considering that fat transfer has been proven as a valuable and easy method to provide scar release. We hypothesized that the combination of fat graft and VLNT to distal site would be more effective than the isolated VLNT for the treatment of breast cancer-related lymphedema by combining the two mechanisms of action of scar release and lymph node transfer. The aim of this study was to retrospectively evaluate and compare surgical and patient-related outcomes in women affected by stage II and III postmastectomy upper limb lymphedema by two approaches: a combined physiological procedure of lymph node flap transfer and release of the axillary scar with fat graft versus only the lymph node transfer.

Patients and methods

Study design and eligibility criteria

The paper is designed as a retrospective comparative study. All patients affected with breast cancer-related upper limb lymphedema operated between January 2012 and January 2016 were retrospectively identified at our department from our institution's digital database.

Inclusion criteria were as follows: (1) History of breast cancer treated with either mastectomy or breast-conserving therapy and axillary lymph node dissection; (2) Stage II and III (International Society of Lymphology staging system)

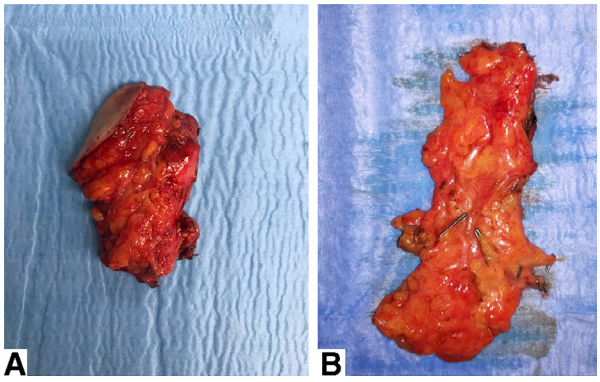

Figure 1 Surgical procedure: harvest of the G-VLN flap (panel A) and the GE-VLN flap (panel B).

breast cancer-related upper limb lymphedema exclusively treated by combined lymph node transfer to distal site and axillary scar release with fat graft or just with lymph node transfer to the distal site. Patients who underwent the ancillary excisional procedure to treat lymphedema were excluded. The diagnosis of lymphedema was made by clinical examination and was confirmed by lymphoscintigraphy in all cases. Group A included patients who underwent a combined procedure (VLNT + fat graft), whereas Group B included patients who underwent only VLNT. Patients' characteristics are summarized in Table 1.

This study was conducted according to the Declaration of Helsinki and the International Society of Lymphology Consensus Document.[30] All participants gave informed written consent.

Surgical procedure

All patients (Group A and Group B) underwent VLNT for the treatment of postmastectomy upper extremity lymphedema. Both groin lymph node flaps (G-VLN) and right gastroepiploic lymph node flaps (GE-VLN) were performed. G-VLN or GE-VLN was transferred to the ventral wrist of the lymphedematous limb (Figure 1). When a GE-VLN was harvested, the recipient site was closed using local flaps.[31]

Group A patients underwent an axillary scar release with an autologous fat graft transferred from the abdomen, at the same time of the VLN flap harvest. Patients received standard tumescent fluid infiltration. Suction-assisted liposuction was performed with a cannula tip of 4 mm diameter. Lipoaspirate was processed through sedimentation and was injected using a 5 mL syringe Luer Lock with a 1.6 mm tip cannula. The adipose tissue fraction was inserted into the dermo-hypodermic junction by the retrograde technique. Through the same incision, many radiating passages were made to distribute the fat in different directions, as this technique seems to allow better fat grafting surgical and minimizes the possibility of forming cysts[32] The treated area was covered with paper patches for 1 week, and patients were instructed to avoid pressure and friction to limit the displacement of the fat (Figure 2).

All patients were monitored postoperatively for 5 days and were discharged between postoperative days 5-6.

Table 1 Patients' demographics and surgical data.

	No. of patients	Age, y (Mean ± SD)	BMI, Kg/m^2 (Mean ± SD)	Diagnosis (n)		Breast Cancer Surgical treatment		Radiotherapy (no. of patients)	Symptom duration, mo (Mean ± SD)	Pre-op lymphedema stage (n)		Flap type (n)		Lymphoscintigraphy, TI value (Mean ± SD)	Follow-up, mo (Mean ± SD)
				LBC	RBC	MAST	BCT			IIb	III	G-VLN	GE-VLN		
Group A (*VLNT+ scar release with fat graft*)	18	56 ± 4	28 ± 3	9	9	13	5	12	26 ± 4	11	7	6	12	20 ± 5	29 ± 4
Group B (*VLNT*)	21	55 ± 5	27 ± 3	12	9	15	6	15	25 ± 3	13	8	14	7	20 ± 4	32 ± 3

LBC: Left Breast Cancer; RBC: Right Breast Cancer; MAST: Mastectomy; BCT: Breast Conservative Therapy; G-VLN: Groin Vascularized Lymph Node Flap; GE-VLN: Right Gastroepiploic Vascularized Lymph Node Flap; TI: Transport Index.

Figure 2 Surgical procedure: axillary scar release with fat grafting, after the inset of the lymph node flap (GE-VLN flap in the illustrated case).

For most patients with lymphedema, manual drainage (physiotherapy) was started on the seventh postoperative day and recommended 3 times a week for a month, followed by 2 times a week for up to 2 months.

Outcomes evaluation

Patients were evaluated at 1, 3, 6, 12, and 24 months. Mean operative time and hospitalization days were collected. At each visit, the following data were collected: circumference measurements, episodes of cellulitis, and Lymphedema Quality of Life (LYMQOL) questionnaire metrics. Circumference measurements were performed at defined intervals (mid hand, wrist, elbow, and 10 cm above and below elbow) by the same trained nurse. Lymphoscintigraphy was repeated 1 year after surgery. Clinical evaluation of donor site morbidity was performed.

Clinical assessment of the treated scars (Group A) with the POSAS[33] was performed before surgical procedure and at 1 year of follow-up.

Surgical and patient-related outcomes between Group A and Group B were compared. The primary outcome measure was the reduction rate (RR) of upper limb circumference (above elbow and below elbow). The circumferential RR was defined as the preoperative difference between the circumferences of the lesion and healthy limbs minus the postoperative difference, divided by the preoperative difference. Secondary outcome measures included the incidence of cellulitis and the specific quality of life parameters.

Statistical analysis

SPSS 25.0 software (SPSS, Inc., Chicago) was used to analyze data. Continuous variables were described as range or mean $\pm$ standard deviation (SD). Mean values of outcome variables of both groups were analyzed using paired Student t-test. Statistical significance was defined as p value < 0.05.

Results

Thirty-nine patients met inclusion criteria (Group A = 18; Group B = 21). The average follow-up time to lymphodynamic evaluation was 29 months (range, 24–38 months) for Group A and 32 months (range 28–44) for Group B. A GE-VLN flap was performed in 19 cases and a G-VLN flap in 20 cases. When a GE-VLN flap was harvested, local flaps were used for closure except in 2 out of 19 patients who underwent small split-thickness skin graft placement taken from the thigh to allow relief of tension and compression over the transferred flap. In 19 out of 39 patients, a surgical revision with the microsurgical debulking technique of the flap and removal of skin graft was performed 1 year after lymph node transfer[34] (Figures 3 and 4).

Surgical results in terms of survival rate of flaps, postoperative lymphoscintigraphy, and donor site morbidity were comparable in both groups. Flap rate survival was 100% after microsurgical transfer in all patients. Postoperative lymphoscintigraphy showed improvement of the lymph flow on the affected limb in all cases. No donor site morbidity was encountered during the follow-up period. The mean operative time and hospitalization days did not show significant difference between the two groups.

At 3 and 6 months of follow-up, the mean RR values at above elbow level were significantly higher ($p<0.0001$) in Group A (25.7 ± 2.5 at 3 months; 35.3 ± 5.9 at 6 months) than in Group B (15.6 ± 1.7 at 3 months, 24.6 ± 2 at 6 months). However, no significant difference was detected when comparing mean RR values above elbow (AE) ($p = 0.6$) and below elbow (BE) ($p = 0.9$) at 12 months postoperatively (Group A, AE: 50.6 ± 6.5, BE: 34.6 ± 6; Group B, AE: 49.6 ± 5.4, BE: 34.5 ± 5.4). The same finding was observed when comparing above elbow (p value=0.6) and below elbow (p value=0.7) RR values at 24 months postoperatively (Group A, AE: 51.3 ± 6.3, BE: 34.8 ± 5.8; Group B, AE: 50.2 ± 5.5, BE: 34.1 ± 5.4). Additionally, no statistically significant difference was observed when comparing the incidence of cellulitis episodes 1 year postoperatively (Group A: 0.4 ± 0.5; Group B: 0.6 ± 0.7; $p = 0.4$) (Table 2; Figure 5).

LYMQOL metrics showed significantly better scores ($p<0.0001$) in all domains (function, appearance, symptoms, and mood) at all follow-up appointments in Group A than in Group B (Figure 6). Furthermore, the scar-treated areas at the axillary fold in Group A showed a qualitative improvement from both an esthetic and a functional point of view (Figure 7). Reduction or complete resolution of pain and increases in scar elasticity were objectively assessable in all cases (Table 3).

Table 2 Surgical outcomes.

	Above elbow RR (Mean ± SD)				Below elbow RR (Mean ± SD)				Infectious episodes/ year (Mean ± SD)	
	3 months	6 months	12 months	24 months	3 months	6 months	12 months	24 months	Pre-op	Post-op (1 y)
Group A (*VLNT+ scar release with fat graft*)	25.7 ± 2.5	35.3 ± 5.9	50.6 ± 6.5	51.3 ± 6.3	13.8 ± 1.6	20.9 ± 2.3	34.6 ± 6	34.8 ± 5.8	3.5 ± 0.9	0.4 ± 0.5
Group B (*VLNT*)	15.6 ± 1.7	24.6 ± 2	49.6 ± 5.4	50.2 ± 5.5	13.9 ± 1.9	21.6 ± 1.5	34.5 ± 5.4	34.1 ± 5.4	3.5 ± 1	0.6 ± 0.7
P value	<0.0001*	<0.0001*	0.6	0.6	0.8	0.3	0.9	0.7	0.9	0.4

VLNT: vascularized lymph node transfer; RR: reduction rate. A *p* value <0.05 was considered significant.

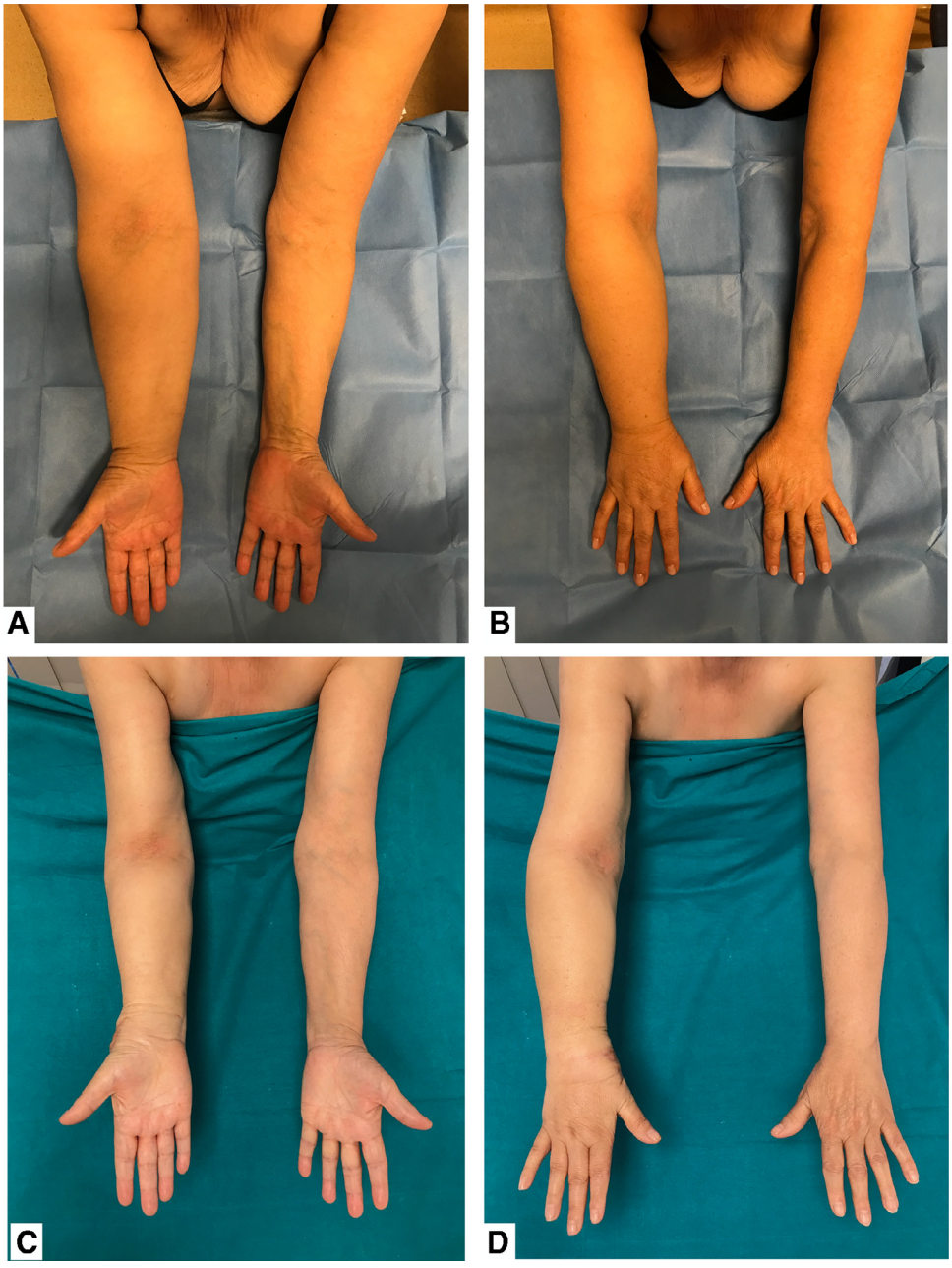

Figure 3 Case no. 7 (Group A) **A-B**. A 59 year-old patient presented with breast-related right upper limb lymphedema (stage III). A combined GE-VLN flap and axillary scar release with fat grafting was planned. **C-D**. Postoperative views at 24 months of follow-up, after debulking of the VLN flap on the right wrist.

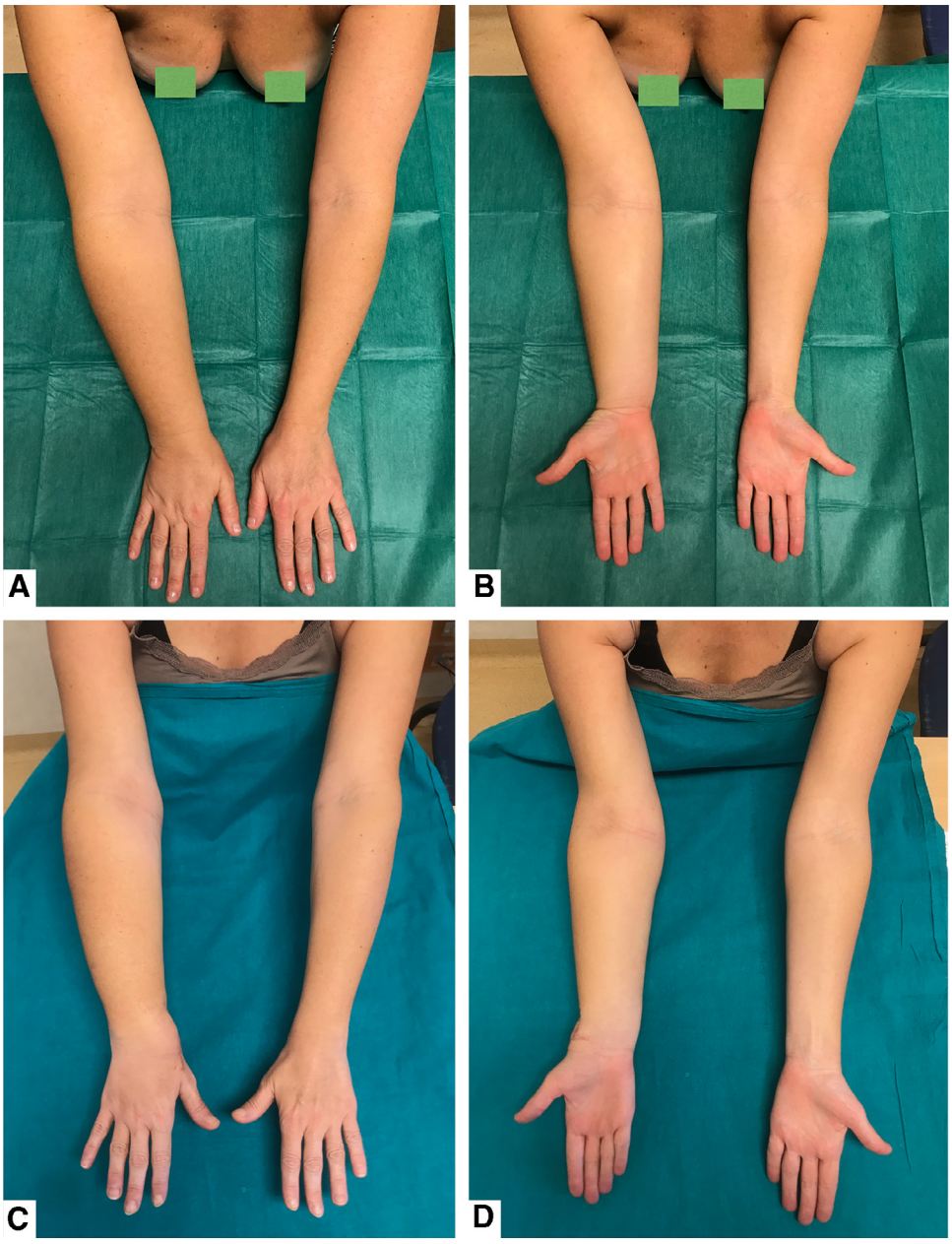

Figure 4 Case no. 10 (Group A) **A-B A** 50 year-old patient presented with breast-related right upper limb lymphedema (stage IIb). A combined left G-VLN flap and axillary scar release with fat grafting was planned. **C-D.** Postoperative views at 24 months of follow-up after debulking of the VLN flap on the right wrist.

Table 3 Clinical preoperative and postoperative values of the treated scar, POSAS parameters at 1 year follow-up in Group A.

Parameter	Mean (preop)	Mean (postop)
Vascularization	2.3	2.1
Pigmentation	5.8	5.3
Thickness	8	6.2
Relief	9	4.5
Pliability	6.3	4.2
Overall	6.7	5.1

Discussion

Upper limb lymphedema can be unfortunate sequelae following the oncologic treatment of breast cancer. Various surgical options exist to decrease the symptom burden of upper limb lymphedema, including VLNT, lymphovenous bypass (LVB), liposuction, lymphatic grafting, and excisional procedures.[20,35] VLNT has shown promising results, and it is becoming one of the mainstay treatment options for extremity lymphedema, with evidence of efficacy from different working groups.[17-24]

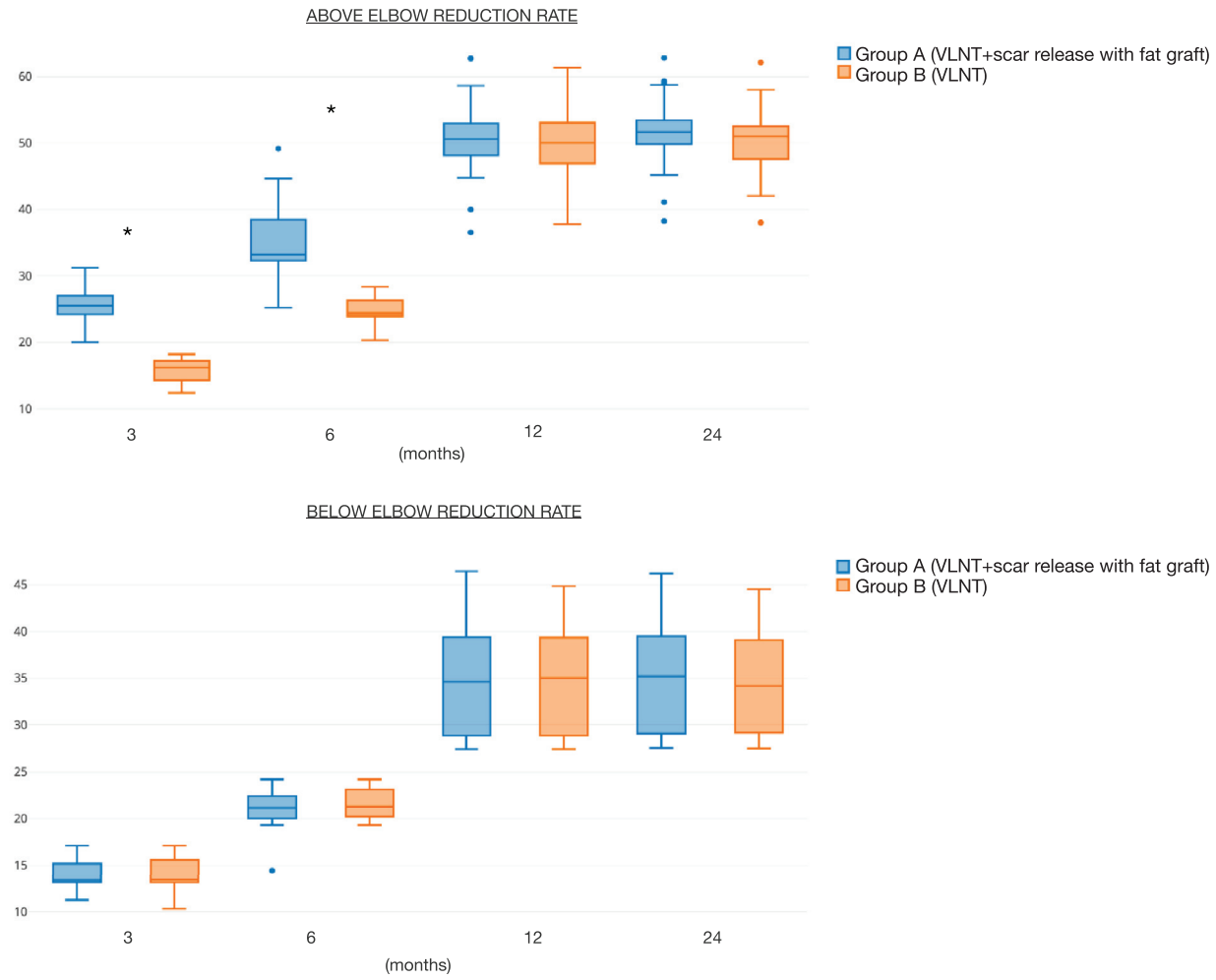

Figure 5 Temporal changes of the mean circumference reduction rates at above and below elbow levels when comparing Group A and Group B. A significant statistical difference can be observed at 3 and 6 months at above elbow measurements ($^{*}p<0.05$).

The idea to perform a scar tissue release with autologous fat graft and vascularized lymph node transfer during the same surgical session to treat postmastectomy upper extremity lymphedema was based on the concept that the two procedures could act at different levels. First, we opted to perform the VLNT to a distal location instead of the lymph node-depleted area. The choice of the recipient site is a topic of debate.[20,36] Patel et al.[20] discussed the efficacy of a distal nonanatomic placement of VLN to provide a sustained limb circumference reduction in extremity lymphedema. Distal VLN transfers may represent the ideal recipient location considering that the progressive changes that occur following proximal injury result in distal lymphatic pump failure. As a matter of fact, the clinical changes are more pronounced in the gravity-dependent portion of the extremity.

Second, the axillary scar in the affected arm was released, as the scar tissue may block the lymphatic flow. The scar release was achieved through autologous fat grafting. From a histological point of view, autologous fat grafts show the ability to regenerate the dermis and subcutaneous tissue and improve the dermal and dermohypodermic quality in scar areas through increases in the fat layer, largely destroyed in cases of thermal insults and poorly regenerated during tissue repair after any type of trauma, new collagen deposition, and local neoangiogenesis.[32,37-42]

The comparison of the surgical outcomes between patients who had undergone a combined procedure (VLNT + scar release with fat graft) and patients who had undergone only VLNT showed interesting results. The RR in Group A at the above elbow level in the early follow-up was significantly higher than that in the control group, suggesting that the axillary scar release with fat graft may have effectively contributed to the improvement of lymph circulation, and the improvement itself is earlier than in those patients who received only VLNT. However, no statistical difference was found later in the follow up (12–24 months). This finding may be explained if we consider the pathophysiology of lymphedema. In the early stages of injury following lymph node dissection, chronic inflammation and subclinical lymphatic fluid stasis promote proliferation and collateralization of capillary lymphatics in the superficial dermis. In the fraction of patients who proceed to develop lymphedema that is clinically measurable,

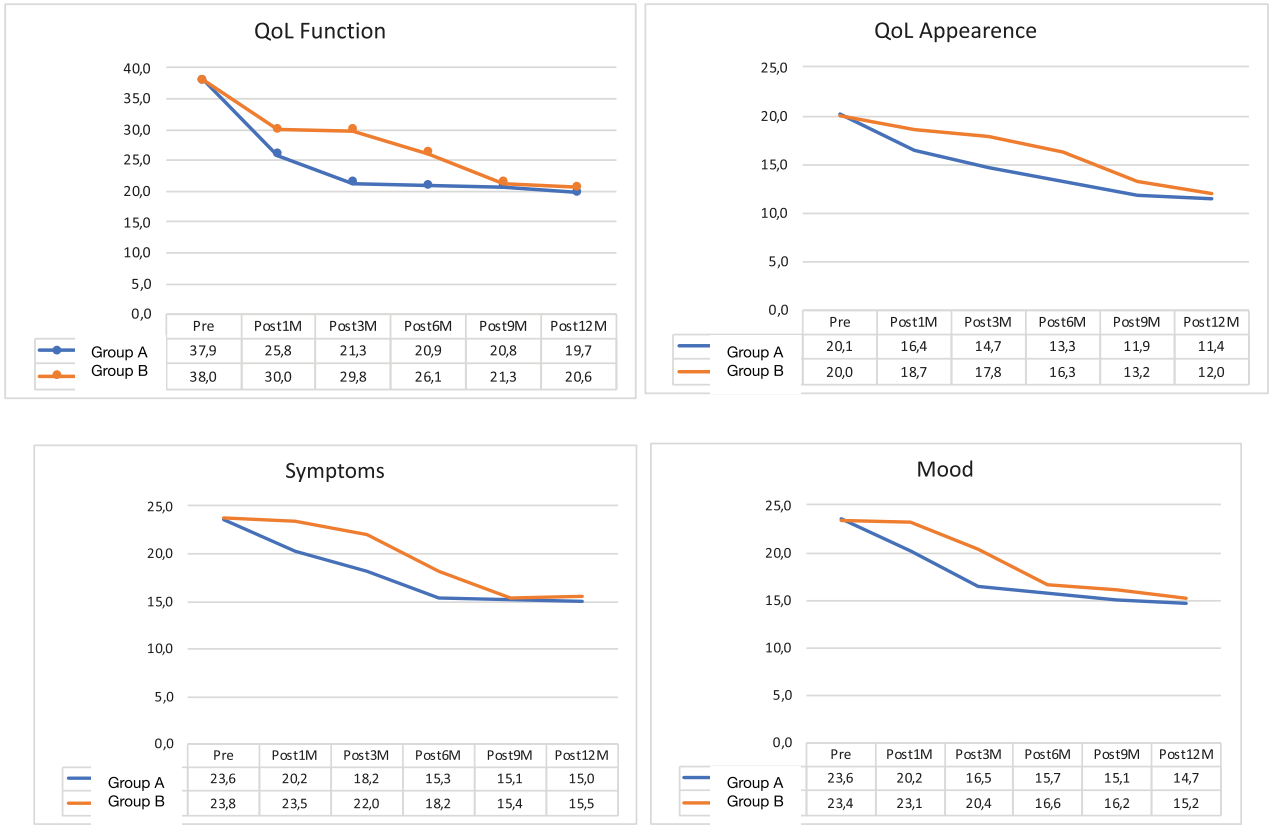

Figure 6 **A-B** Case no. 10 (Group A). Pre- and postoperative views of the axillary fold, showing an esthetic qualitative improvement of the treated scar.

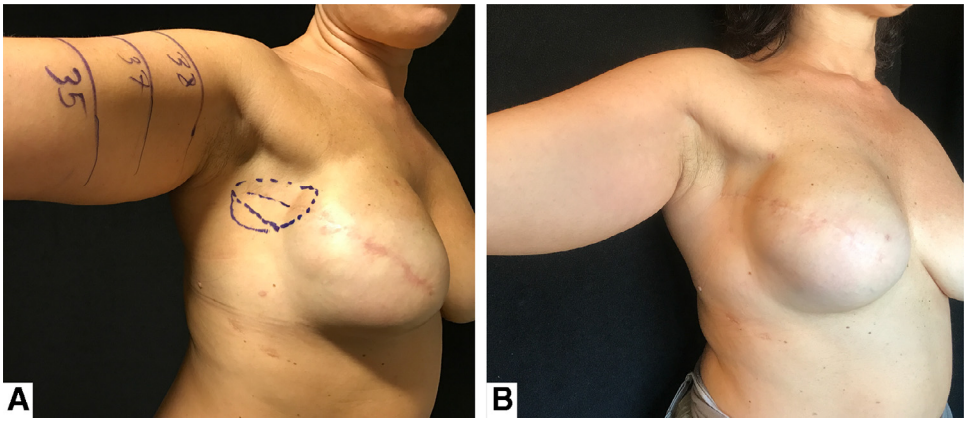

Figure 7 Temporal changes to LYMQOL-specific domains in lymphedema patients when comparing Group A and Group B. Gradual improvement in the reported scores can be observed for each domain within each group. A statistically significant difference ($p<0.05$) between the two groups can be observed in all domains at every follow-up evaluation.

sustained interstitial fluid stasis and ongoing chronic inflammation lead to extracellular matrix collagen deposition with resultant obliteration of capillary lymphatics and smooth muscle proliferation around collecting lymphatics. It is possible that the procedure of scar release will act on the still reversible lymphatic fluid stasis related to the presence of an obstacle, namely, the scar itself. However, because we are dealing with patients with stage II and III lymphedema, an additional maneuver is needed to drain all the collected fluid and make the surgical intervention stable over time. This is the role of VLNT, and this explains why the difference between the two groups of patients sorts out over time.

Furthermore, the fast patient-observable difference in terms of limb circumference and scar appearance and symptoms in Group A patients may justify the significant improvement in all LYMQOL domains. On the other hand, the fact that no significant difference was observed in terms of infection rates among the two groups could be

predictable, as the VLNT procedure has been associated with a possible effect on the impaired immune response noted in lymphedema.[43]

The work has some limitations related to the sample size. The strict criteria of inclusion and exclusion (post mastectomy upper limb lymphedema, stages II and III) can favor the development of further studies, with a bigger sample and a longer follow-up.

Conclusions

Breast cancer-related upper limb lymphedema is a common and still unsolved problem. Although the series presented herein is not large, it is the first series reporting the use of a combined VLNT and scar release with fat graft for the treatment of moderate-stage breast cancer-related lymphedema. The efficacy, even only in the short-term follow-up, in fastening the limb circumference reduction and improving patient-related surgical outcomes makes it reasonable to think that this approach could be useful for the treatment of postmastectomy upper limb lymphedema, adding only little time and costs to the overall surgical procedure. We advocate further larger research to corroborate and expand the results of the study.

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