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ORIGINAL ARTICLE – RECONSTRUCTIVE ONCOLOGY

A Prospective Evaluation of Lymphedema-Specific Quality-of-Life Outcomes Following Vascularized Lymph Node Transfer

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ABSTRACT

Background. Microsurgical techniques for the treatment of lymphedema rapidly increased in popularity. Although surgical success with vascularized lymph node (VLN) transfer has been demonstrated, limited studies have investigated the influence of microsurgical treatments on health-related quality-of-life (HRQoL) parameters. The aim of this study was to prospectively evaluate changes in HRQoL following VLN transfer for upper- and lower-extremity lymphedema using a validated instrument.

Methods. An Institutional Review Board-approved prospective study was performed of patients who underwent VLN transfer for symptomatic upper- or lower-limb lymphedema. A validated lymphedema-specific questionnaire—lymphoedema quality-of-life study—was utilized to assess specific quality-of-life parameters at multiple time points during the 12-month perioperative period. For a comparison with HRQoL metrics, limb circumference measurements were obtained to assess circumference differentiation.

Results. Twenty-five patients met the study criteria. Limb circumference analysis revealed significant early improvements following VLN transfer, with continued improvement during the study period (upper-limb lymphedema: 24.4 %; lower-limb lymphedema: 35.2 %). These improvements were mirrored by improvements in all HRQoL domains and overall quality of life ($p < 0.01$). The function, body appearance, symptom, and mood domains were all found to be significantly improved during the postoperative evaluation, with continued improvement being reported throughout the study period ($p < 0.01$ within each domain).

Conclusions. Microsurgical treatment of lymphedema with VLN transfer procedures effectively decrease limb circumference. This improvement is mirrored by improvements in patient-reported outcomes and quality of life. These changes can be observed as soon as 1 month postoperatively, and continued steady improvement can be expected.

Lymphatic microsurgical procedures are becoming increasingly popular for the treatment of chronic and debilitating symptoms related to lymphedema. Vascularized lymph node (VLN) transfer and lymphovenous anastomosis (LVA) continue to be the most common microsurgical techniques related to the surgical treatment of this condition.[1,2]

Health-related quality-of-life (HRQoL) metrics have changed patient expectations and treatment protocols in the setting of breast,[3,4] head and neck,[5] and lower-extremity reconstruction.[6] Outcomes following conservative and non-surgical lymphedema treatments have focused on objective measurements, with limb circumference being the predominant benchmark used for comparative evaluations. In addition, various studies have evaluated aspects of microsurgical procedures for lymphedema. In reference to VLN transfer, preoperative surgical planning,[7] technical refinements to flap dissection,[8] recipient site preference,[9] and optimization of surgical results with the reduction of limb circumference[10] have been the focus of many studies. HRQoL measurements have been evaluated in many aspects of lymphedema treatment,[11–14] but there is little understanding of these patient-centered metrics in relation to lymphatic microsurgery, particularly VLN transfer

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procedures. The purpose of this study was to prospectively evaluate these patient-centered metrics over time in patients undergoing VLN transfer for upper- and lower-limb lymphedema.

PATIENTS AND METHODS

Study Population and Design

A prospective Institutional Review Board-approved, single-institution study was performed with approval from the Chang Gung Hospital Research Ethics Board. The enrollment eligibility period was from January 2005 to July 2013. A single research coordinator (C-YL) was responsible for patient enrollment, administration of questionnaires, and collection of data.

Patients were eligible for enrollment if they had symptomatic lymphedema of the upper or lower limb. The majority of patients possessed late-grade disease, and only those who were determined to be eligible for VLN transfer were included. Surgical procedures included both vascularized groin and submental lymph node flap transfers to distal recipient sites (lower limb, ankle/knee; and upper limb, wrist/elbow). Patients were excluded if they underwent combined procedures involving debulking, liposuction and/or lymphovenous bypass during the study period.

Surgical Technique

Prior to surgery, all patients underwent Tc^{99} lymphoscintigraphy to confirm the presence of lymphatic drainage obstruction. In addition, lymphodynamic evaluation with indocyanine green (ICG) injection was performed to assess the severity of dermal backflow and the presence of open, functional lymphatic vessels in order to determine if lymphovenous shunting procedures could be performed prior to VLN transfer.

The VLN donor site was chosen based on surgeon preference and a preoperative Doppler ultrasound study evaluating the quantity of sizable lymph nodes.[15] Early procedures were performed with the groin VLN flap, but later procedures involved the use of the submental VLN flap. An increased lymph node number and a thin, soft tissue area are characteristics of the preferred donor site.[15] Free tissue harvest was performed, with careful attention to maintaining soft tissue and vascular connections between the flap and lymph nodes, and all flaps included a skin paddle for monitoring. Distal extremity recipient sites were used for all flaps. Proximal, anatomic sites were not used in any patient as they were not the preferred site of the senior author based on the catchment-effect principle and the effects of gravity. Microsurgical anastomosis was typically performed in an end-to-end fashion to the arterial and superficial and/or deep venous systems. Intraoperative ICG fluorescence was used to confirm the presence of intrinsic lymphovenous connections within the flap and donor venous drainage to ensure optimal postoperative lymphatic fluid drainage. Standard postoperative flap monitoring was performed to guarantee flap viability, and the routine hospital stay was approximately 2 weeks. Following hospital discharge, patients were encouraged to ambulate, slowly increase daily activity, and eliminate any previous compression therapy. Prior to a patient's surgical referral, protocols for complex decongestive therapy (CDT) were not consistent as the majority of patients were referred from outside of the hospital system. Following surgery though, a strict protocol was strongly recommended to all patients. All protocols involved the complete elimination of wrapping, compression, and/or other physiotherapy. Clinic visits were routinely performed on a monthly basis during the first year. During each visit, the research coordinator performed limb circumference measurements. In addition, HRQoL assessments were conducted during predetermined intervals, as discussed below.

Data Collection and Demographics

Perioperative details and demographics were collected for all included patients. The outcomes of interest included limb circumference, excess circumference reduction rates, and HRQoL metrics comprehensively assessed with a lymphedema-specific questionnaire. Preoperative characteristics evaluated included patient age, BMI, lymphedema stage, etiology, length of symptoms prior to surgical treatment, and the occurrence of cellulitis. Limb circumference measurements were obtained at two and three different locations along the length of an upper and lower extremity, respectively. On the upper limb, circumferential tape measurements were performed at 10 cm above and below the elbow joint. On the lower limb, measurements were made on the thigh and proximal leg at 15 cm proximal and distal to the lower border of the patella, and at 10 cm proximal to the lateral malleolus. Limb circumference measurements were obtained at each follow-up visit. The circumferential differentiation was defined as the circumference of the diseased limb subtracted from that of the healthy limb, and divided by that of the healthy limb.[10] A modified lymphedema grading system was introduced based on symptom severity, circumferential differentiation, patency of lymphoscintigraphy, and related available reconstructive options (Table 1). Briefly, VLN transfer is indicated for grade 2–4 lymphedema patients.

TABLE 1 Grading Scale for the Surgical Treatment of Lymphedema

Grade	Symptoms	Circumference differentiation (%)	Lymphoscintigraphy	Management
0	Reversible	<9	Partial occlusion	CDP
I	Mild	10–19	Partial occlusion	LVA, liposuction, CDP
II	Moderate	20–29	Total occlusion	VLN transfer, LVA
III	Severe	30–39	Total occlusion	VLN transfer + additional procedures
IV	Very severe	>40	Total occlusion	Charles procedure + VLN transfer

Circumference differentiation: circumference of the lesioned limb subtracted from the circumference of the healthy limb and divided by the circumference of the healthy limb, which is measured at 10 cm above and below the elbow, 15 cm above and below the knee, and 10 cm above the ankle

CDP complex decongestive physiotherapy, *LVA* lymphaticovenous anastomosis, *VLN* vascularized lymph node

TABLE 2 Patient Characteristics

Edema part Variables	Upper-limb lymphedema	Lower-limb lymphedema
No. of patients	15	10
Age	53.1 ± 9.7	55.9 ± 8.9
Lymphedema grading (%)		
I	0	10
II	26.7	20
III	60	40
IV	13.3	30
BMI	25.5 ± 3.8	27.9 ± 3.9
Symptom duration	37.1 ± 30.5	95.7 ± 135.5
Cellulitis occurrence (times/year)		
Preoperative	3.5 ± 3.3	6.4 ± 5.8
Postoperative	0.7 ± 0.9	0.5 ± 0.7
Conservative therapy duration	18.2 ± 21.9	30.1 ± 20.7
Type of surgery [*n* (%)]		
VGLN	13 (86.7)	0
VSLN	2 (13)	10 (100)
Follow-up (range)	25.4 ± 8.4	16.1 ± 4

Data are expressed as mean ± SD unless otherwise stated

BMI body mass index, *VGLN* vascularized groin lymph node, *VSLN* vascularized submental lymph node

Lymphedema-Specific Questionnaire

Only patients with a minimum of 12 months of follow-up following surgery were evaluated, and only questionnaires administered at the specified time points and associated evaluations were used for this study to normalize comparison between patients. The lymphoedema quality-of-life study (LYMQOL) is a condition-specific, validated questionnaire used to assess the effectiveness of lymphedema-related treatment plans.[16] Two specific modules exist within the questionnaire, each of which are designed to address the upper or lower limb. The upper-limb module is comprised of 27 questions, while the lower-limb module consists of 26 questions. Each module is designed to assess four specific quality-of-life domains as well as an overall quality-of-life score. The four domains include function, appearance, symptoms, and mood. Each domain is scored from 1 to 4, with 1 representing a response of 'not at all', and 4 representing a response of 'a lot'. Overall quality-of-life scores were assessed on a scale of 1–10, with higher scores indicating a higher-rated overall quality of life.

Each questionnaire was administered at six time points during the perioperative period. Following preoperative assessment and consent for VLN transfer, the LYMQOL questionnaire was administered in person by a single research coordinator (C-YL). During the postoperative period, questionnaires were administered at 1, 3, 6, 9, and 12 months. Patients were evaluated in an office setting and the questionnaires were administered at that time.

Statistical Analysis

Statistical analysis was performed using SPSS version 18.0 statistical software (SPSS, Inc., Chicago, IL, USA.). The Mann–Whitney *U* test was used for comparisons of non-parametric data. A p value ≤ 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

During the 8.5-year study period, 58 patients were identified as undergoing lymphatic microsurgical procedures; 25 met the study inclusion criteria and completed 150 questionnaires. Patient demographics are shown in Table 2. Fifteen patients were included in the upper-limb cohort, and 10 were included in the lower-limb cohort. The majority of cases of upper- and lower-limb lymphedema were secondary to postoncologic surgery (93.1 %), while a few were either congenital or idiopathic in nature (6.9 %).

TABLE 3 Upper ($n = 15$) and lower ($n = 10$) extremity (follow-up 12 months)

	Upper extremity			Lower extremity		
	Preoperative	Follow-up 12 months	p value	Preoperative	Follow-up 12 months	p value
Circumferential differentiation	18.1 ± 4.2	12.1 ± 5.3	0.03	26.2 ± 13.2	16.1 ± 14.1	<0.01
Circumferential reduction rate	–	24.4 ± 14.7	–	–	35.2 ± 23.9	–
Cellulitis occurrence (times/year)	3.5 ± 3.3	0.7 ± 0.9	0.05	6.4 ± 5.8	0.5 ± 0.7	<0.01
Overall quality of life (0–10)	2.1 ± 0.5	5.8 ± 0.7	<0.01	3.0 ± 0.1	7.1 ± 0.3	<0.01
Function domain (10–40)	37.9 ± 0.5	19.3 ± 4.4	<0.01	30.0 ± 0.2	16.8 ± 5.3	<0.01
Appearance domain (5–20)	19.9 ± 0.5	12.1 ± 2.9	<0.01	27.6 ± 0.8	17.1 ± 4.1	<0.01
Symptom domain (6–24)	23.9 ± 0.5	15.3 ± 2.8	<0.01	19.6 ± 0.8	12.4 ± 2.9	<0.01
Mood domain (6–24)	23.9 ± 0.5	14.4 ± 2.9	<0.01	23.6 ± 0.8	10.0 ± 1.9	<0.01

In the upper-limb cohort, late-grade disease (grade 3 or 4) was present in the majority of enrolled patients (73.3 %). In addition, the average duration of symptoms was 37.1 months, with patients having undergone conservative therapy for an average of 18.2 months prior to surgical intervention (Table 3). In the lower-limb cohort, late-stage disease was present in the majority of enrolled patients (70 %). The average symptom duration was 95.7 months, and conservative therapy was attempted for the treatment of lymphedema for an average of 30.1 months.

Clinical and Objective Outcomes Following Vascularized Lymph Node Transfer

Overall, there were no partial or complete flap losses, amounting to a 100 % flap success rate. In the upper-limb cohort, circumference differentiation was found to improve as early as 1 month following surgery (17.2 % reduction; $p = 0.05$). These results were sustained and continued to improve throughout the 12-month evaluation period, with an overall reduction rate of 24.4 % (Table 3). This finding was mirrored by a significant improvement in the overall quality-of-life score (2.1–5.8; $p < 0.01$). Similarly, in the lower-limb cohort, sustained and continued improvement in the circumference differential was found as early as 3 months, with an overall reduction rate over the 12-month evaluation period of 35.2 % (Table 3). In addition, the occurrence of cellulitis was significantly decreased in both cohorts (upper limb: $p = 0.05$; lower limb: $p < 0.01$). These findings correlated well with the improvements in the overall quality-of-life scores (3.0–7.1; $p < 0.01$).

Upper Limb Health-Related Quality-of-Life (HRQoL) Assessment

During preoperative evaluation, domain-specific scores indicated significant morbidity associated with lymphedema. In all four domains analyzed (Table 2), average patient-reported scores nearly reached the maximum value for each domain (function: 37.9/40; appearance: 19.9/20; symptoms: 23.9/24; and mood: 23.9/24), indicating near-maximal patient-reported scores for each question. Considering the findings with regard to the function domain obtained during the study period (Fig. 1a), an improvement in reported functionality can be observed as soon as 1 month following surgery ($p < 0.01$), with continued and sustained improvements occurring throughout the 1-year follow-up period ($p < 0.01$). Similarly, significant and sustained improvements were observed in all other HRQoL domains (Figs. 1b, c, d), with some occurring as early as 3–6 months following surgical intervention. For the 12-month evaluation period, significant improvements in all HRQoL domains were observed in addition to the global reported overall QoL ($p < 0.01$ for all domains).

Lower Limb HRQoL Assessment

Evaluation of the lower-limb cohort revealed similar trends as those observed in the upper limb patient population. The preoperative HRQoL scores indicated high levels of morbidity and functional impairment, with high scores reported for each domain (function: 30/32; appearance: 27.6/28; symptoms: 19.6/20; and mood: 23.6/24) (Table 3). Evaluation of domain-specific changes over time (Figs. 2a–d) revealed significant changes that occurred as early as 3 months following surgery (mood), while most domain-specific changes were observed at 6–9 months following VLN transfer (symptoms, appearance, and function). A specific comparison of the preoperative assessment and 12-month assessment revealed significant improvements in the scores for all domains ($p < 0.01$) (Fig. 2; Table 3).

DISCUSSION

The circumferential reduction in upper-limb lymphedema was 24.4 ± 14.7 %, with a mean follow-up of 25.4 ± 8.4 months, while the circumferential reduction in

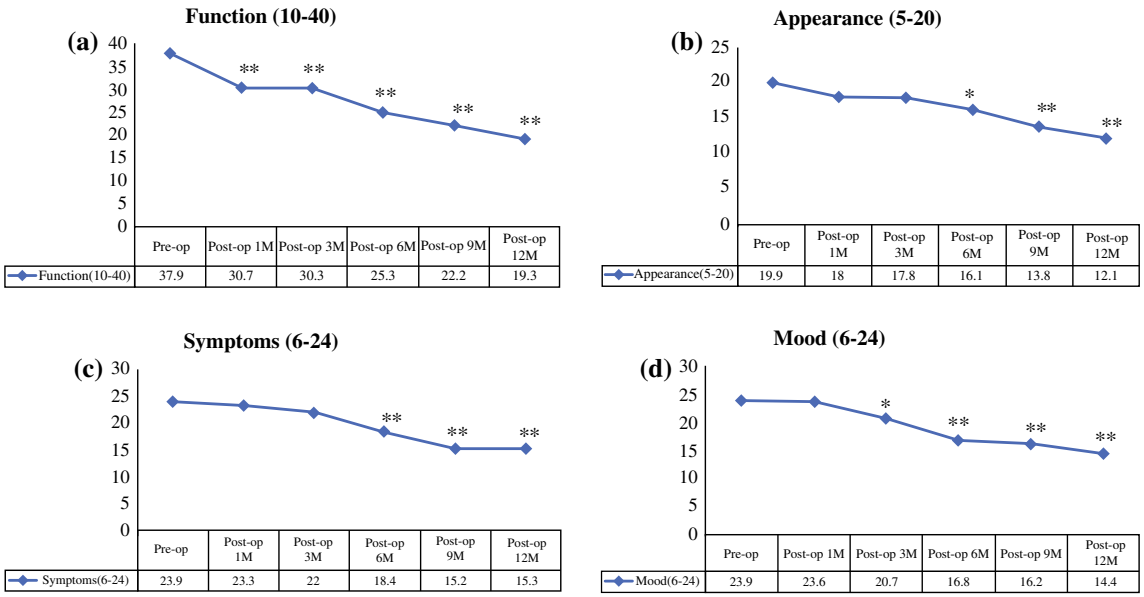

FIG. 1 Temporal changes to HRQoL-specific domains in upper-limb lymphedema patients. The average reported scores of each domain are represented. Gradual and steady improvements in the reported scores can be observed within each domain (**a**, **b**, **c**, **d**). Functionality was significantly improved at the 1-month postoperative evaluation (**a**), with significant improvements occurring in all other domains at the 3- and 6-month evaluations (**b**, **c**, **d**). *HRQoL* health-related quality of life, *pre-op* preoperative, *post-op* postoperative, *xM* *x*-month, $*p \leq 0.05$, $**p < 0.01$

lower-limb lymphedema was 35.2 ± 23.9 %, with a mean follow-up of 16.1 ± 4 months. One of the three possible explanations for this observation may be the inherent difference in disease progression in the upper and lower extremity. Or a more simplistic explanation may be related to the observation of more perceived dramatic improvements in more advanced cases, as seen in our series, with the lower-extremity cohort having a higher preoperative circumference difference. If this were the case, the observed reduction rate would be greater. Third, the gravity effect of transferred VLN likely has more of an impact in lower-limb lymphedema, therefore the improvement in lower-limb lymphedema may be more significant compared with upper-limb lymphedema.

Understanding quality-of-life outcomes following reconstructive procedures are paramount in defining success following treatment. For the treatment of lymphedema, various management protocols exist. Nonsurgical therapy has been the mainstay of treatment of this condition for decades. Several previous studies have validated specific protocols and treatment strategies for nonsurgical therapy.[17–20] Newer techniques related to lymphatic microsurgery, particularly VLN transfers, are being increasingly described as novel and effective adjuncts for the treatment of lymphedema. Four studies have reported the efficacy of this novel treatment option for various stages of upper- and lower-limb lymphedema.[9,10,21,22] Although variations in specific techniques have been described, the overall basis for this therapy involves the transfer of lymph nodes with blood supply to a lymph node-depleted region. Processes related to lymphangiogenesis[23] and neo-lymphatic pumping[24] have been proposed as relevant mechanisms of action that allow for lymphatic fluid clearance.

Multiple HRQoL instruments have been used to assess lymphedema treatments.[25,26] General assessment tools, such as the disability of the arm, shoulder and hand (DASH),[14] short-form (SF)-12[27] SF-36,[12] and other region-specific tools[19,28] have been used to gauge morbidity in relation to the occurrence of lymphedema and/or treatment protocols. Although lymphedema-specific assessment tools exist,[25,26] few studies have distinctively addressed the impact of surgical treatment on lymphedema-specific HRQoL outcomes. The LYMQOL is a condition-specific instrument that can be used to track changes in quality of life throughout an upper- or lower-limb lymphedema treatment. For this reason, it was considered an appropriate instrument to use in our assessment.

Understanding patient-centered metrics such as the HRQoL assessment significantly contributes to the utility and validity of VLN transfer techniques. Although improvements in objective measurements, such as that of limb circumference, have achieved measureable and comparable value for use in follow-up evaluations, defining success following VLN transfer is multifactorial. Reductions in both patient limb circumference and limb volume closely mirror improvements in patient function and quality of life. In the clinical setting, definite improvements in

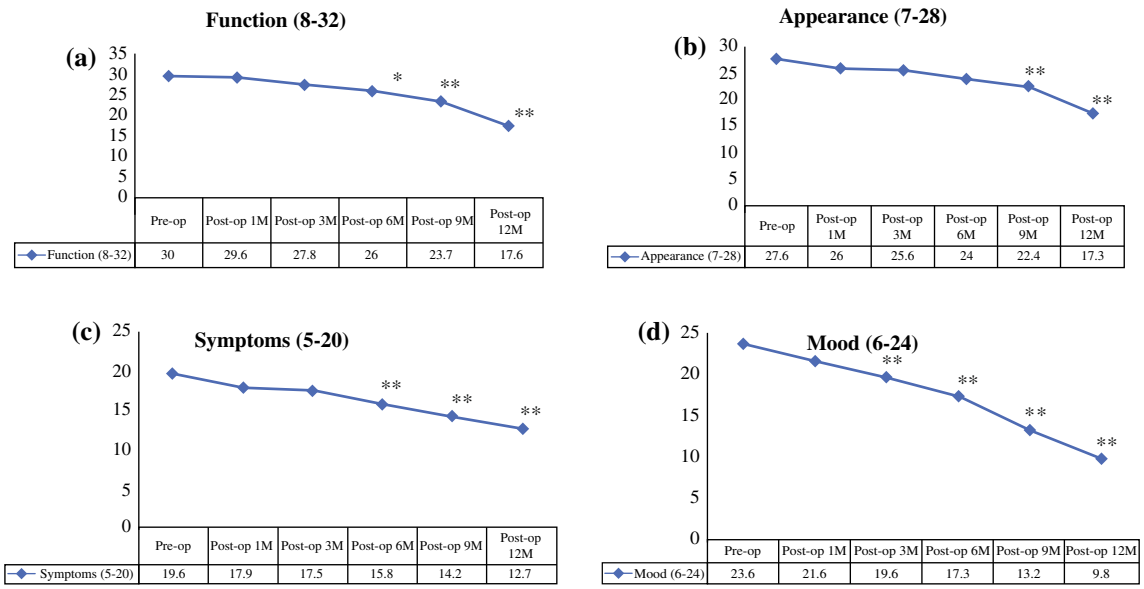

FIG. 2 Temporal changes of HRQoL-specific domains in lower-limb lymphedema patients. Gradual and steady improvements in all domains (**a**, **b**, **c**, **d**) can be detected throughout the 1-year evaluation. Early significant improvements were seen in the symptoms (6 months) and mood (3 months) domains (**c**, **d**) compared with the function (9 months) and appearance (9 months) domains (**a**, **b**). *HRQoL* health-related quality of life, *pre-op* preoperative, *post-op* postoperative, *xM* *x*-month, $*p \leq 0.05$, $**p < 0.01$

measureable limb circumference have been observed. Interestingly, many patients who reported appreciable changes in activity levels have described subjective improvements in limb 'heaviness' following surgical treatment. In turn, this leads to increased activity levels by the patient, adding to the complexity of the assessment of limb circumference. These observations underscore the importance of a multifactorial approach to outcomes assessment.

The assessment of HRQoL metrics indicated that some domains improved earlier than others. Functionality showed a rapid improvement following surgery in the upper-limb cohort compared with the lower-limb cohort (1 vs. 6 months, respectively). This finding may represent intrinsic differences in the development of upper- and lower-limb lymphedema. On the other hand, it may simply represent differences in the chronicity of disease prior to surgical intervention. In addition, marked improvements in functionality occurred prior to patients' self-perceptions of limb appearance improvements. This finding suggests that improvements in functionality may occur before a noticeable difference in the clinical appearance of the limb because subtle decreases in volume likely yield dramatic improvements in the patients' perception of limb weight and usability.

CONCLUSIONS

The clinical and patient-centered outcomes assessment validated the use of VLN transfer procedures in the treatment of extremity lymphedema. To our knowledge, this study is the first prospective evaluation of patient-reported outcomes related to VLN transfer procedures. Outcomes assessment following surgical treatment of lymphedema should be approached in a multifactorial way.

Psychosocial and functional improvements following the development of upper- and lower-limb lymphedema are possible with VLN transfer. Improvements in HRQoL domains can be appreciated early and appear to correlate well with improvements in limb circumference measurements within the first post-surgical year.

DISCLOSURES None.

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