http://dx.doi.org/10.1590/0100-6991e-20192156

Original Article

Influence of vascularized lymph node transfer (VLNT) flap positioning on the response to breast cancer-related lymphedema treatment.

Influência do posicionamento do retalho linfonodal vascularizado na resposta ao tratamento cirúrgico do linfedema secundário ao câncer de mama.

Eduardo Montag[1,2]; Alberto Yoshikazu Okada[1,2]; Eduardo Gustavo Pires Arruda[1,2]; Alexandre Siqueira Fonseca[1,2]; Miluska Bromley[1]; Alexandre Mendonça Munhoz[1,2]; Fábio Freitas Busnardo[1,2]; Rolf Gemperli, TCBC-SP[2].

1. Institute of Cancer of the State of São Paulo (ICESP) Service of Plastic Surgery, São Paulo, SP, Brazil.
2. University of São Paulo, Faculty of Medicine, Discipline of Plastic Surgery, São Paulo, SP, Brazil.

ABSTRACT

Objective: to evaluate the initial therapeutic experience of transplantation of vascularized lymph nodes in patients with lymphedema of the upper limbs secondary to the treatment of breast cancer, and to verify if the positioning of the transplant influences the surgical result. **Methods**: we conducted a prospective, comparative test of two therapeutic modalities, with 24 patients with lymphedema of the upper limb after breast cancer treatment, classified as grades 2 and 3, according to the International Lymphedema Society. The two types of procedures performed were: 1) total breast reconstruction with - deep inferior epigastric perforator (DIEP) flap associated with lymph node flap, in patients with no previous breast reconstruction or loss of previous reconstruction (axillary positioning); 2) isolated inguinal lymph node flap performed in patients with completed breast reconstruction or without the desire to perform the breast reconstruction (wrist positioning). **Results:** the reduction percentage of the affected limb volume was 20.1% (p=0.0370). The number of infectious episodes (cellulites) also decreased significantly, from 41% in the preoperative period to 12.5% in the postoperative one (p=0.004). There

were no differences between the proximal and distal groups. **Conclusion:** the transplantation of lymph nodes positively affected the postoperative evolution of patients with lymphedema secondary to breast cancer. We observed no differences in relation to flap positioning.
Keywords: Lymphedema. Breast Cancer Lymphedema. Surgical Flaps. Upper Extremity.

INTRODUCTION

Patients treated for breast cancer, especially those undergoing axillary dissection and radiotherapy, may progress with lymphedema, a chronic, progressive and debilitating condition. Its occurrence significantly worsens the quality of life of such patients and may generate psychosocial problems[1-6]. The accumulation of lymph in the tissues induces chronic inflammation and fibrosis, which causes deposition of fat in the affected limb. The standard treatment for lymphedema is composed of the association of manual lymphatic drainage, compression, and bandages[7], with good response, especially in patients with early degrees of disease. Patients with more advanced degrees present absent or poor response to medical treatment, with progression of the edema, pain, and repeated infections in the affected limb[8]. This particular group of patients may be candidates for surgical treatment.

Two types of procedures may be used to treat lymphedema. The procedures for reducing volume[9-11], such as liposuction or Charles operation, exhibit great effectiveness in volume loss but are reserved for patients with a nonfunctioning lymphatic system[12]. The other type is composed of physiological procedures that aim to reestablish the function of the lymphatic system and interrupt the vicious cycle that leads to its destruction and the progression of the disease. The latter comprise the lymphatico-venular anastomosis (LVA) and the lymph nodes vascularized transplant. LVA is a technically complex procedure that requires not only training in supermicrosurgery[13-15] by the surgeon, but also specific sutures and material. The availability of lymphangiography with indocyanine green is also of fundamental importance for the diagnosis and placement of anastomoses in areas adjacent to the point of obstruction of the lymphatic system[7].

On the other hand, microsurgeons without specific training in supermicrosurgery are enabled to perform the lymph node transplantation, introduced by Chen *et al.* and O'Brien *et al*.[16,17] for the treatment of obstructive lymphedema in a canine model. Several positioning techniques have been described for transplanted lymph nodes, such as in the armpit, elbow and wrist[18-20]. Different success rates have been described for the various

methods and the available literature presents heterogeneous results regarding patient selection and surgical techniques[21].

In the present study, we prospectively evaluated our initial experience with lymph node transplantation in 24 consecutive patients with upper limb lymphedema secondary to treatment of breast cancer.

METHODS

This is a prospective, comparative cohort of 24 patients with upper limb lymphedema secondary to breast cancer treatment at the Cancer Institute of the State of São Paulo (ICESP), from January 2014 to December 2018. Patients were informed about the investigative nature of the study and signed an informed consent form.

Inclusion criteria were patients with lymphedema stages 2 or 3, according to International classification Society of Lymphedema (ISL), with a duration of at least six months, not responding to complex decongestive therapy. Exclusion criteria were progression of the underlying disease (breast cancer), active episode of infection at the time of surgery, scars in the lymph nodes donor area, and loss of the flap. After inclusion in the study, we cataloged the patients in a database and submitted them to the surgical procedure in our institution.

Patients underwent circumferential measurements of both upper limbs at six fixed points: at the wrist and at regions five and ten centimeters above it, and at the elbow and at regions five and ten centimeters above it[22]. We calculated the limb volume using the truncated cone formula ($v= pr^2.(h/3)$)[23]. We repeated the measurements postoperatively after one, three, six, 12, 18 and 24 months. All patients were referred to the Rehabilitation Department for preoperative evaluation.

We performed two types of procedures: 1) Total breast reconstruction with deep inferior epigastric perforator (DIEP) flap associated with the lymph node flap, carried out in patients without previous reconstruction or with a history of loss of reconstruction (axillary positioning); and 2) isolated inguinal lymph node flap, performed in patients with completed breast reconstruction or without the desire to undergo breast reconstruction (wrist positioning) (Figure 1).

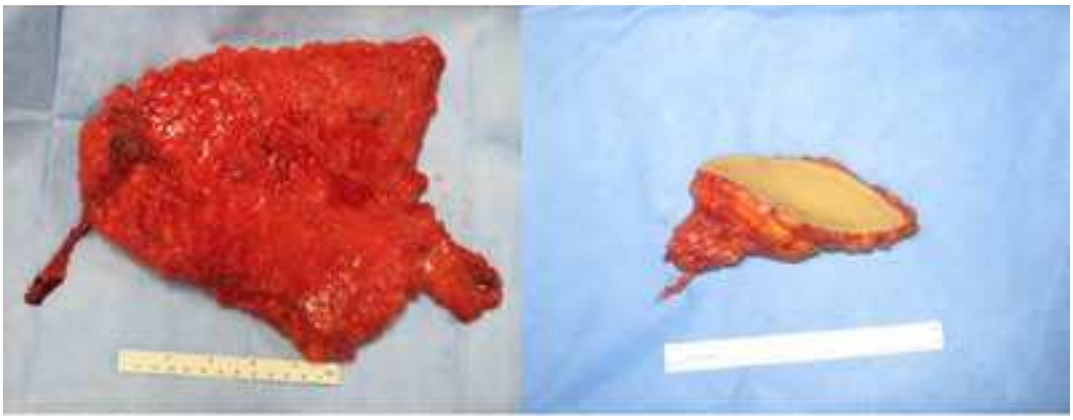

Figure 1. Abdominal flap with associated lymph nodes (left). Inguinal flap with lymph nodes (right).

Surgical Technique

Abdominal flap

The abdominal flap was dissected and vascularized by the pedicle of the deep inferior epigastric artery, with total or partial preservation of the abdominal wall musculature. Prior to the start of the surgery, we injected blue dye in the thigh to allow identification of the lymph nodes that drained the limb, preventing their use and consequent secondary lymphedema in the donor area. Through block dissection, we resected the lymph nodes contained in the subcutaneous tissue located between the superficial epigastric and superficial iliac circumflex vessels, together with the abdominal flap. During flap dissection, a second surgical team prepared the receiving area. We resected the axillary scar and adequately exposed the vessels. In all cases, the primary receptors were the internal thoracic vessels (artery and vein). We performed a second venous anastomosis in the axilla to ensure adequate venous drainage of the flap. After positioning of the main flap, the lymph node flap was allocated in the axilla. We applied continuous suction drains in both the donor and receiver areas. Postoperative monitoring was performed with three-hour intervals for the first 48 hours and every six hours until hospital discharge, on the fifth postoperative day.

Inguinal flap

Before the flap was elevated, we performed the same patent blue injection, as previously described. The flap vascular axis was marked 2cm below the inguinal ligament, lateral to the common femoral artery. A small skin ellipse was marked on the vascular axis of the flap. The dissection started at the upper margin of the flap and continued lateral to medial after identification of the pedicle. We made no maneuver to identify or individualize

the lymph nodes, so as to avoid damage to the lymphatic tissue. The recipient areas chosen were the dorsal or volar portion of the wrist, as previously described by Cheng *et al*.[20]. We made a transverse access in wrist skin fold, and dissected the subcutaneous plane to accommodate the flap containing the lymph nodes. We performed the vascular anastomoses to the dorsal metacarpal branch of the radial artery and its comitant veins. We sutured the skin without tension whenever possible. When necessary, we used a small skin graft to reduce tension or a left portion of the flap without suture, to heal by second intention. The dressing included the use of plaster cast for 21 days with the wrist in a neutral position to avoid traction in the vascular pedicle. Postoperative monitoring was performed at three-hour intervals in the first 48 hours and every six hours until hospital discharge, on the fifth postoperative day.

After withdrawing the drainage, we referred the patients to the rehabilitation sector to resume complex decongestive therapy and compression. This occurred after 30 postoperative days. The postoperative returns were, respectively, at one, three, six, 12, 18 and 24 months. We repeated measurements in all visits in both the normal and unaffected limbs. Cellulitis/erysipelas episodes were clinically diagnosed by erythema, edema and pain in the affected limb, and treated for 14 days with a first-generation cephalosporin.

We characterized the variables as mean, median, standard deviation and confidence interval. We analyzed outcomes using the Fischer exact test and the Wilcoxon and Mann Whitney tests. We considered a p-value <0.05 with 80% power as statistically significant. We used the Stata v15.0 software (StataCorp LLC, College Station, TX, USA) in the statistical analysis.

The study was approved by the Ethics in Research Committee of ICESP (protocol nº 24096813.2.1001.0065) and conducted according to the Helsinki Declaration.

RESULTS

We included 24 patients in the study. The mean age was 52.8 years (38-68, SD=8.89). Regarding the type of breast cancer treatment, 15 patients (68%) underwent mastectomy associated with axillary emptying of levels I, II and III; five (22%) underwent mastectomy and emptying of levels I and II; and three (9%) underwent segmental resection and axillary emptying of levels I to III. Regarding the lymphedema stage, six patients (12. 5%) presented grade 1 lymphedema; 15 (62.5%), grade 2; and five (25%), grade 3 lymphedema. The median time to the onset of lymphedema after surgery was 13.12 months (range: 2-53, SD=12.36); the mean time between diagnosis and surgical treatment was 43.6 months (range: 5-170, SD=47.61). Regarding the treatment method,

15 patients (62%) underwent breast reconstruction associated with lymph node transplantation into the axilla, while nine (37.5%) underwent transplantation to the wrist region (Table 1).

Table 1. Baseline characteristics

Patient	Age (years)	Breast cancer treatment	Lymphedema grade (ISL)	Type of treatment	Affected side	Interval until lymphedema (months)	Duration of illness (months)
1	50	Mastectomy + axillary emptying of levels 1 to 3	2	LNT*	R	8	15
2	67	Mastectomy + axillary emptying of levels 1 to 3	2	LNT	R	3	13
3	41	Mastectomy + axillary emptying of levels 1 to 3	2	LNT	R	10	16
4	48	Mastectomy + axillary emptying of levels 1 to 3	1	LNT	R	5	11
5	45	Setorectomy + emptying of levels 1 to 3	1	LNT	R	6	17
6	53	Mastectomy + axillary emptying of levels 1 to 3	2	LNT	R	22	6
7	47	Mastectomy + axillary emptying of levels 1 to 3	3	DIEP** + LNT	L	30	45
8	54	Mastectomy + axillary emptying of levels 1 to 3	3	LNT	R	14	5
9	59	Setorectomy + emptying of levels 1 to 3	2	DIEP + LNT	L	24	120
10	38	Mastectomy + axillary emptying of levels 1 to 3	3	DIEP + LNT	L	8	34
11	54	Mastectomy + axillary emptying of levels 1 and 2	2	LNT	R	4	17
12	43	Mastectomy + axillary emptying of levels 1 and 2	1	LNT	R	13	14
13	68	Mastectomy + axillary emptying of levels 1 to 3	3	DIEP + LNT	L	53	37
14	40	Mastectomy + axillary emptying of levels 1 and 2	2	DIEP + LNT	L	3	21
15	47	Mastectomy + axillary emptying of levels 1 and 2	2	LNT	R	12	12
16	41	Mastectomy + axillary emptying of levels 1 and 2	2	LNT	R	21	14
17	53	Mastectomy + axillary emptying of levels 1 to 3	2	DIEP + LNT	L	36	168
18	58	Mastectomy + axillary emptying of levels 1 to 3	3	LNT	R	6	60
19	62	Setorectomy + emptying of levels 1 to 3	2	DIEP + LNT	L	3	32
20	58	Mastectomy + axillary emptying of levels 1 to 3	3	DIEP + LNT	L	8	170
21	57	Mastectomy + axillary emptying of levels 1 to 3	2	LNT	R	7	46
22	63	Mastectomy + axillary emptying of levels 1 to 3	2	LNT	R	7	24
23	57	Mastectomy + axillary emptying of levels 1 to 3	2	DIEP + LNT	L	10	96
24	65	Mastectomy + axillary emptying of levels 1 to 3	2	LNT	R	2	47

* LNT: lymph node transplantation; ** DIEP: deep inferior epigastric perforator flap.

We evaluated the circumferences and volumes of both upper limbs before surgery and compared them with the measurements in the 18-month postoperative period. table 2 shows the mean volumes of normal and affected limbs in the preoperative period and at 18 postoperative months. The mean volume loss was 20.1% (range: -66% to 90%, SD=44.89%). The Wilcoxon test showed statistical significance (p=0.0370).

Table 2. Mean volume, preoperatively and 18 months after surgery.

Preoperative Volume		Postoperative volume (18 months)		Percentage loss	*p*
Healthy member	Affected member	Healthy member	Affected member		
1704cm^3	2293cm^3	1704cm^3	2228cm^3	20.1%	0.0370

Figure 2 shows the volumetric differences between the limbs (healthy *versus* affected) before (blue) and after (green) the surgical treatment. The preoperative median was 426cm^3, ranging from 53cm^3 to 1296cm^3, and the interquartile range (IQR) was 300cm^3 (25%) to 774cm^3 (75%). The median after 18 months postoperatively was 425cm^3, with a range of 5cm^3 to 1021cm^3, and IQR of 192cm^3 (25%) to 661cm^3 (75%).

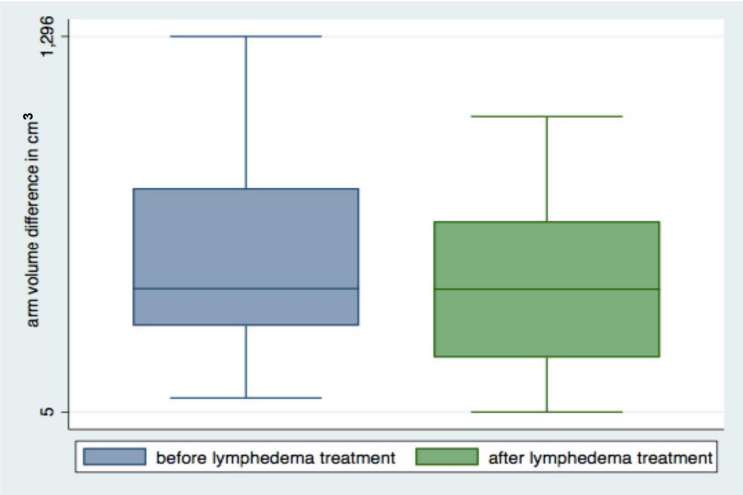

Figure 2. Boxplot comparing volumes preoperatively and 18 months after surgery.

We evaluated the presence of cellulitis before and after treatment. Table 3 shows the presence of infectious episodes six months before and six months after treatment. Before surgery, ten patients (41%) presented cellulitis six months before surgery with a mean of 2.1 episodes. After treatment, three patients (12.5%) had episodes of cellulitis, with a mean of 0.2 episodes. Patients without previous history of infection did not present infectious episodes in the postoperative period. The Wilcoxon test demonstrated a statistically significant (p=0.004) reduction in the number of infectious episodes after six months of follow-up.

Table 3. Cellulitis episodes six months before and six months after surgical treatment.

	Patients	Average episodes	Maximum number of episodes	Standard deviation	*p*
12 months preoperatively	10	2.1	3	0.875	0.004
12 months postoperatively	2	0.2	1	0.421	

Table 4 shows the affected limb volumes and infection episodes of groups DIEP + lymph node transplant and lymph node alone. The Mann Whitney U tests (p=0.428) and the Fischer exact test (p=0.582) showed no differences between the groups analyzed.

Table 4. Comparison of limb volume and cellulitis episodes between groups.

Variable	Surgical technique	Averages	Frequency	P
Limb volume difference	DIEP* + LNT**	20.6% volume reduction		0.4208
	Isolated LNT	19.3% volume reduction	.	
Cellulitis episodes	DIEP + LNT	-	Preoperative: 7 Postoperative: 0	0.582
	Isolated LNT	-	Preoperative: 14 Postoperative: 2	

* DIEP: deep inferior epigastric perforator flap; ** LNT: lymph node transplantation.

DISCUSSION

The present study prospectively evaluated our clinical experience with vascularized lymph node transplantation in 24 patients with upper limb lymphedema secondary to breast cancer treatment. The onset of lymphedema occurs after removal of axillary lymph nodes followed or not by radiotherapy. This leads to a reduction in lymphatic transport velocity and pressure increase in the lymphatic system, which causes an increase in interstitial pressure in the limb and damages the remaining lymphatic channels, creating a vicious cycle that continuously worsens the condition[24-26].

There is evidence that vascularized lymph node transplant is an important technique for the treatment of secondary lymphedema and can be effective in stopping the disease progression and reduce limb volume by 20% of the preoperative volume. There are two proposed mechanisms of action for lymph node transplantation. The flap can act as a "sponge", absorbing the excess fluid due to the pressure gradient between the affected limb and the flap[18,20,27], and the liquid is then drained into the venous system, functioning as a shunt between the lymphatic and the venous systems. The second mechanism is possible only in cases where the lymph nodes are positioned in the axilla, in which the scar tissue resection exposes the previously clogged lymphatic channels to the flap tissue, allowing rebuilding of the routes formerly lost.

Recurrent infections such as cellulitis/erysipelas are common and potentially serious infections in patients with lymphedema. The relationship between episodes of infection and lymphedema is a vicious circle: the deterioration in lymphatic function predisposes to episodes of infection that in turn damage even more the lymphatic system, causing worsening of the condition and facilitating the occurrence of new outbreaks of infection. Lymph node transplantation works to decrease infection episodes by reducing

the edema present in the affected limb, and improving bacterial clearance, with consequent improvement in immune function. The patients reported reduction in the number of infection episodes and we observed no infections in patients with no infectious history prior to the procedure. We also observed that transplantation of vascularized lymph nodes allowed the treatment of onychomycosis not responsive to the preoperative drug treatment in two patients. In addition, eight patients reported improvement in limb range of motion after surgery. The prevalence of chronic pain was common in the studied sample. In theory, lymphatic stasis and increased tissue pressure would lead to a constant stimulation of the sensory nerves, causing pain[28]. There have been previous reports of pain improvement after lymph node- venous anastomoses[28].

One study stated that lymph node transplantation is superior to lymphatic-venous anastomosis and to complex decongestive therapy in relation to circumferential loss and infectious episodes[29]. There is no consensus on the best positioning for the lymph node flap. Distal transplantation is an option in more advanced cases, since it does not depend on ascending lymph flow and counts on the action of gravity to function. Axillary positioning is the obvious choice from a physiological point of view. It allows the release of the axillary scar, leading to a reduction of venous pressure in the affected limb, in addition to allowing gain of range of motion and recanalization of the previously lost lymphatic pathway. The disadvantage lies in the need of a patent lymphatic system with upward flow against gravity, allowing lymph transport to the transplanted lymph node flap, hence the importance of the armed propaedeutics, which allows for conduct individuation. The comparative analysis between volume reduction of treated limbs and number of infectious episodes did not demonstrate significant differences related to lymph node positioning. This fact suggests that patients and surgeons can jointly make the choice of flap placement, according to their respective preferences. Further studies with larger series are needed to corroborate this finding.

The limitations of this study are the small series and the lack of randomization. Nevertheless, after analyzing the initial experience there is evidence that transplantation of vascularized lymph nodes is effective in the treatment of lymphedema secondary to breast cancer in the three stages of ISL classification. The number of infectious episodes declined in most patients. New studies will be conducted to evaluate the impact of treatment on improving patients' quality of life and to establish the best positioning of the lymph node flap for the best functional results, although the preliminary results have not demonstrated advantages between the axillar or distal positioning groups.

RESUMO

Objetivo: analisar a experiência terapêutica inicial do transplante de linfonodos vascularizados em pacientes portadoras de linfedema de membros superiores secundário ao tratamento do câncer de mama e verificar se o posicionamento do transplante influencia o resultado cirúrgico. **Métodos:** ensaio prospectivo, comparativo, de duas modalidades terapêuticas em 24 pacientes portadoras de linfedema de membro superior após tratamento de câncer mamário, classificados como graus 2 e 3, segundo a Sociedade Internacional de Linfedema. Os dois tipos de procedimentos realizados foram: 1) reconstrução total da mama com retalho de perfurante da artéria epigástrica inferior (DIEP- deep inferior epigastric perforator flap) associado ao retalho linfonodal, em pacientes sem reconstrução mamária prévia ou com histórico de perda da reconstrução (posicionamento axilar); 2) retalho linfonodal inguinal isolado foi realizado em pacientes com reconstrução mamária finalizada ou sem o desejo de realizar a reconstrução da mama (posicionamento no punho). **Resultados:** a porcentagem de redução do volume do membro afetado foi de 20,1% (p=0,0370). O número de episódios infecciosos (celulites) também sofreu redução significativa, de 41% no período pré-operatório para 12,5% no pós-operatório (p=0,004). Não se observou diferenças entre os grupos proximal e distal. **Conclusão:** o transplante de linfonodos afetou positivamente a evolução pós-operatória de pacientes portadoras de linfedema secundário ao câncer de mama. Não foram observadas diferenças em relação ao posicionamento do retalho.

Descritores: Linfedema. Linfedema Relacionado a Câncer de Mama. Retalhos Cirúrgicos. Extremidade Superior.

ACKNOWLEDGE

The authors would like to acknowledge Dr. Edward Chang for the contribution in the review of the paper.

REFERENCES

1. Fu MR, Kang Y. Psychosocial impact of living with cancer-related lymphedema. Semin Oncol Nurs. 2013;29(1):50-60.
2. Fu MR, Rosedale M. Breast cancer survivors' experiences of lymphedema-related symptoms. J Pain Symptom Manage. 2009;38(6):849-59.
3. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. Psychooncology. 2013;22(7):1466-84.

4. Chachaj A, Malyszczak K, Pyszel K, Lukas J, Tarkowski R, Pudelko M, et al. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. Psychooncology. 2010;19(3):299-305.
5. Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol. 2009;27(12):2007-14.
6. Fu MR. Women at work with breast cancer-related lymphoedema. J Lymphoedema. 2008;3(1):20-5.
7. Oliveira MMF, Gurgel MSC, Amorim BJ, Ramos CD, Derchain S, Furlan-Santos N, et al. Long term effects of manual lymphatic drainage and active exercises on physical morbidities, lymphoscintigraphy parameters and lymphedema formation in patients operated due to breast cancer: A clinical trial. PLoS One. 2018;13(1):e0189176.
8. Lin CH, Ali R, Chen SC, Wallace C, Chang YC, Chen HC, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. Plast Reconstr Surg. 2009;123(4):1265-75.
9. Sistrunk WE. Contribution to plastic surgery: removal of scars by stages; an open operation for extensive laceration of the anal sphincter; the kondoleon operation for elephantiasis. Ann Surg. 1927;85(2):185-93.
10. Charles RH. Elephantiasis Scroti. London: Churchill; 1912.
11. Homans J. The treatment of elephantiasis of the legs: A preliminary report. N Engl J Med. 1936;215(24):1099-104.
12. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2009 Consensus Document of the International Society of Lymphology. Lymphology. 2009;42(2):51-60.
13. Koshima I, Kawada S, Moriguchi T, Kajiwara Y. Ultrastructural observations of lymphatic vessels in lymphedema in human extremities. Plast Reconstr Surg. 1996;97(2):397-405; discussion 406-7.
14. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S, Fujitsu M. Minimal invasive lymphaticovenular anastomosis under local anesthesia for leg lymphedema: is it effective for stage III and IV? Ann Plast Surg. 2004;53(3):261-6.
15. Koshima I, Narushima M, Yamamoto Y, Mihara M, Iida T. Recent advancement on surgical treatments for lymphedema. Ann Vasc Dis. 2012;5(4):409-15.

16. Chen HC, O'Brien BM, Rogers IW, Pribaz JJ, Eaton CJ. Lymph node transfer for the treatment of obstructive lymphoedema in the canine model. Br J Plast Surg. 1990;43(5):578-86.
17. O'Brien BM, Hickey MJ, Hurley JV, Dvir E, Khazanchi RK, Pederson WC, et al. Microsurgical transfer of the greater omentum in the treatment of canine obstructive lymphoedema. Br J Plast Surg. 1990;43(4):440-6.
18. Lin CH, Ali R, Chen SC, Wallace C, Chang YC, Chen HC, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. Plast Reconstr Surg. 2009;123(4):1265-75.
19. Becker C, Assouad J, Riquet M, Hidden G. Postmastectomy lymphedema: long-term results following microsurgical lymph node transplantation. Ann Surg. 2006;243(3):313-5.
20. Cheng MH, Chen SC, Henry SL, Tan BK, Lin MC, Huang JJ. Vascularized groin lymph node flap transfer for postmastectomy upper limb lymphedema: flap anatomy, recipient sites, and outcomes. Plast Reconstr Surg. 2013;131(6):1286-98.
21. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. Plast Reconstr Surg. 2014;133(4):905-13.
22. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Phys Ther. 2006;86(2):205-14.
23. Yakamoto N, Yakamoto T, Hayashi N, Hayashi A, Lida T, Koshima I. Arm volumetry versus upper extremity lymphedema index: validity of upper extremity lymphedema index body-type corrected arm volume evaluation. Ann Plast Surg. 2016;76(6):697-9.
24. Viitanen TP, Mäki MT, Seppänen MP, Suominen EA, Saaristo AM. Donor-site lymphatic function after microvascular lymph node transfer. Plast Reconstr Surg. 2012;130(6):1246-53.
25. Guyton AC, Barber BJ. The energetics of lymph formation. Lymphology. 1980;13(4):173-6.
26. Bates DO, Levick JR, Mortimer PS. Subcutaneous interstitial fluid pressure and arm volume in lymphoedema. Int J Microcirc Clin Exp. 1992;11(4):359-73.
27. Cheng MH, Huang JJ, Nguyen DH, Saint-Cyr M, Zenn MR, Tan BK, et al. A novel approach to the treatment of lower extremity lymphedema by transferring a

vascularized submental lymph node flap to the ankle. Gynecol Oncol. 2012;126(1):93-8.
28. Mihara M, Hara H, Zhou HP, Tange S, Kikuchi K. Lymphaticovenous anastomosis releases the lower extremity lymphedema-associated pain. Plast Reconstr Surg Glob Open. 2017;5(1):e1205.
29. Engel H, Lin CY, Huang JJ, Cheng MH. Outcomes of lymphedema microsurgery for breast cancer-related lymphedema with or without microvascular breast reconstruction. Ann Surg. 2018;268(6):1076-83.

Received in: 02/11/2019
Accepted for publication: 03/20/2019
Conflict of interest: none
Source of funding: none

Mailing address:
Eduardo Montag
E-mail: e.montag@hc.fm.usp.br