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Donor-site safety in microvascular lymph node transfer for breast cancer-related lymphedema using reverse lymphatic mapping—A prospective study

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Summary *Background:* Vascularized lymph node transfer (VLNT) is one option among other surgical treatments in the management of breast cancer-related lymphedema (BCRL). The cause of concern regarding VLNT harvested from the groin has been the potential development of secondary lower-extremity lymphedema. This study explored the risks associated with donor-site morbidity following groin VLNT, with or without concomitant breast reconstruction.
Method: The cohort comprised data from the Lymfactin® Phase I and II trials, conducted from 2016 to 2019, that used perioperative reverse lymphatic mapping. The volume of the lower extremities was measured preoperatively and at 3, 6, and 12 months postoperative, and the adverse events were documented during study visits.
Results: Altogether, 51 women with a mean age of 55.5 years were recruited. The mean duration of BCRL was 31.8 months. Among these, 25 (49%) underwent VLNT (VLNT-group) and 26 (51%) underwent VLNT in combination with breast reconstruction (VLNT-BR group). The groups were similar in terms of age, ($p = 0.766$), BMI ($p = 0.316$), and duration of BCRL ($p = 0.994$).

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Across a period of one year, the volume difference between the lower extremities changed by 22.6 ml (range: −813 to 860.2 ml) ($p = 0.067$). None of the patients had lower-extremity volume difference exceeding 10% at the 12-month follow-up visit. The most frequent adverse events were postoperative pain (17.7%), wound healing issues (11.8%), and seroma formation (11.8%). Most adverse events (64.6%) were classified as minor.

Conclusions: This prospective study demonstrated that groin VLNT with reverse lymphatic mapping appears safe and does not increase the risk of secondary donor-site lymphedema within one year postoperatively.

Patients undergoing axillary lymph node dissection and radiotherapy as part of their oncological breast cancer treatment face an increased risk of developing breast cancer-related lymphedema (BCRL), that affects approximately 20% of patients in this group.[1] The introduction of microsurgery has expanded the therapeutic options for managing BCRL, including vascularized lymph node transfer (VLNT) and lymphavenous anastomosis (LVA), by providing potential anatomical repair of lymphatic drainage.[2–6] The groin VLNT, initially described by Clodius et al. in 1982, marked the first instance of using a VLNT flap to treat lymphedema.[7] This surgical approach relies on a flap on the superficial and deep branch perforators of the superficial circumflex iliac vessels. For post-mastectomy patients with BCRL, microvascular breast reconstruction can be performed using a deep inferior epigastric artery perforator (DIEP) flap in combination with groin VLNT.[3]

There has been a debate regarding the use of the groin as the donor site for VLNT due to the rare but severe complications that can manifest as secondary lymphedema in the lower extremity.[8–10] These complications result from harvest or injury to the lymph nodes and vessels responsible for draining the lower extremities during flap dissection.[8,11] In recent years, new imaging modalities, such as reverse lymphatic mapping, and advancements in surgical techniques aimed at avoiding dissection of the medial femoral vessels have enhanced the safety of the VLNT procedure.[8,12] Previous studies have reported various donor-site complications, including seroma, wound problems, pain, and numbness in the donor-site extremity after groin VLNT flap dissection.[9,10]

This prospective study aimed to investigate the risk of secondary lymphedema in donor-site extremities and morbidities following groin VLNT surgery, with or without concomitant breast reconstruction with free abdominal flap, using perioperative reverse lymphatic mapping.

Methods and patients

The study protocols were approved by the Finnish Medical Agency (FIMEA), ethics committee of the Helsinki Hospital District, Swedish Medical Products Agency, regional ethics committee, and National Medical Board of Sweden. The study identifier numbers for the clinical trials are NCT02994771 and NCT03658967.

The study used data from the Lymfactin® Phase I and II trials,[13] and both the multicenter prospective studies were conducted in Helsinki, Turku, and Tampere (Phase I and II) University Hospitals in Finland and Karolinska and Uppsala (Phase II) University Hospitals in Sweden. Phase I was an open-label, dose-escalation study evaluating the safety, tolerability, and biodistribution of the vector as a single dose of Lymfactin® in patients with BCRL.[13] Phase II was a double-blind, placebo-controlled, randomized study assessing the efficacy, safety, and tolerance of Lymfactin®. Recruitment occurred between 2016 and 2019. Female patients aged 18–70 years with BCRL associated with the treatment of breast cancer at the initial stage N1-N2a and those who had undergone sentinel lymph node biopsies or axillary lymph node dissection were eligible for inclusion in the study. Detailed inclusion and exclusion criteria are presented in Figure 1.

Study visits and measurements

All participants provided written informed consent. Demographic data were recorded preoperatively. This study primarily focused on donor-site morbidity. Detailed protocols have been previously published.[13,14] Trained research staff conducted lower extremity volume measurements using the technique described by Brorson[15] before the operation and during the follow-up study visits at 3, 6, and 12 months postoperatively.

Extremity volumes were calculated by measuring the circumference at 4 cm intervals, with segment volumes determined using the truncated cone formula and total volume derived by summing the individual segment volumes. The total volume of both extremities and volume change difference between the donor and non-donor extremities were calculated at each study visit. A negative value indicated a smaller volume in the donor site extremities. A volume difference of $> 10\%$ in the lower extremities was considered clinically significant, suggestive of potential secondary lymphedema.[16]

Adverse event recording (complications of the donor site and lower extremities)

A comprehensive physical examination was performed by a physician, and adverse events (AEs) and serious adverse events (SEAs) at the donor sites were recorded at all study

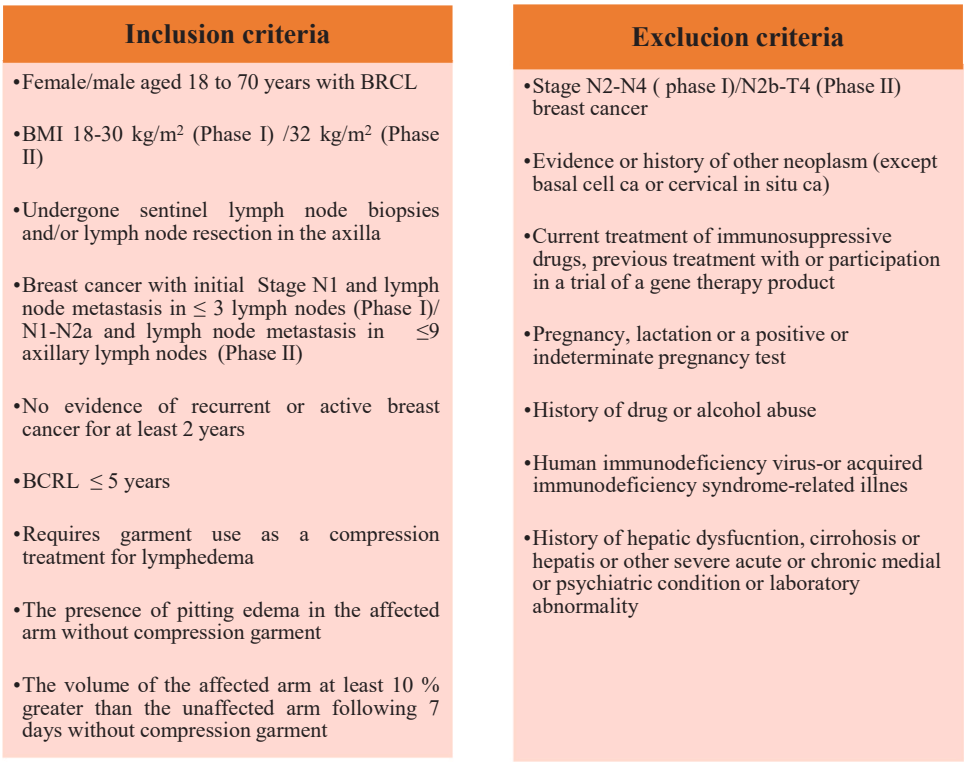

Figure 1 Inclusion and exclusion criteria for Lymfactin® Phase I and II studies.

visits for up to 12 months postoperatively and graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.[17] Patients also kept a diary between visits to report adverse events at the flap donor site and symptoms in the lower extremities.

Operative technique

The surgical procedure involved a two-team approach with the simultaneous raising of the VLNT or VLNT-BR flap while preparing the recipient vessels. Preoperative CT angiography was performed to identify the DIEP flap perforators. If the internal mammary vessels were used as the recipient vessels for the DIEP flap, the VLNT flap was harvested from the opposite side as the chosen DIEP flap perforators and was anastomosed to the thoracodorsal vessels. If the main trunk of the thoracodorsal vessel was used, the VLNT flap was anastomosed to the serratus branches.[3] In the case of the sole VLNT flap, it was raised from the contralateral side to the axilla, where the lymph node flap was anastomosed. The VLNT flap contains lymphatic tissue, draining the lower abdominal wall, including the lymph nodes, lymphatic vessels, and groin fat tissue, based on the superficial circumflex iliac artery perforator (SCIP). There was no preoperative imaging of the lymph nodes. Patent blue (injected intradermally at the level of crista iliaca) was used in most centers to aid visualization of lymph nodes and lymphatics in the flap. The VLNT flap dissection began with lymphatic tissue preparation. The superficial circumflex iliac artery (SCIA) was preoperatively identified and marked using a Doppler ultrasound device. The flap was elevated from lateral to medial at the muscular aponeurosis level, avoiding dissection medial to the femoral vessels. After identifying the deep branch perforator of SCIA, access was gained through the fascia of the sartorius muscle. The VLNT flap remained connected with the DIEP flap at the level of the superficial epigastric vessel pedicle. The superficial circumflex iliac vessels were ligated at their origin, and the superficial epigastric artery and vein were ligated above the inguinal ligament if present. Finally, the DIEP flap was elevated as previously described,[3] and blood perfusion in the VLNT flap was assessed before ligating the main pedicle. The VLNT-BR flap features dual vascular pedicles, including the deep inferior epigastric and superficial circumflex iliac vessels.

Perioperative reverse lymphatic mapping was a crucial step in this procedure, enabling the identification of the critical lymph nodes responsible for draining the lower extremities. Specifically, lymph nodes harvested with the VLNT flap should test negative for the reverse sentinel marker. Mapping involved the injection of a technetium isotope (99mTc-Nanocoll; GE Healthcare) along with gamma imaging using a handheld gamma detector (various brands) or indocyanine green (Verdye, Diagnostic Green GmbH, Germany) in conjunction with near-infrared fluorescence imaging (Photodynamic Eye, Hamamatsu Japan). Before harvesting the flap, 10-20 MBq of 99mTc or 5-10 mg (5 mg/ml) of indocyanine green was injected intradermally in the toe webspace of the donor extremity. Imaging after five to ten minutes identified the lymph nodes responsible for lower extremity lymphatic drainage. These lymph nodes were preserved, and those identified as negative during reverse lymphatic imaging were harvested.[12,18] Imaging was repeated after identifying the vascular pedicle of the flap.

After surgery, the patients were closely monitored and typically discharged between the fifth and seventh

postoperative days. Closed suction drains were placed in the abdominal and lymph node flap harvesting areas and removed when the drainage volume fell below 40 ml per day. As part of their posttreatment care, patients also wore compression pants or other compressive garments around the donor extremity.

Statistical analyses

Statistical analyses were performed using IBM® SPSS® Statistics version 27 and GraphPad Prism 8.0 (GraphPad Software Inc., CA, USA). The D'agostino-Pearson normality test were used to assess data normality. The Wilcoxon test was used to analyze volume data, and the Pearson's correlation was used to examine the relationship between excess volume, age, and BMI changes. Repeated ANOVA was used to analyze volume changes and the chi-squared test was used to compare VLNT and VLNT-BR groups. Linear and logistic regression analyses explored patient-specific factors linked to volume changes and adverse events.

Results

Patients' characteristics

A total of 51 women with a mean age of 55.5 ± 7.7 years (range: 29 to 68 years) were included in this study. Details of 15 patients were requested from the Lymfactin® Phase I trial and 36 from the Phase II trial. The mean BMI remained consistent over time (pre-op 27.5 ± 3.4 kg/m^2 and at 12-month post-op; 27.5 ± 3.6 kg/m^2, p = 0.953). The mean duration of BCRL was 31.8 ± 13.2 months (range: 9 to 62 months). A total of 25 (49%) and 26 (51%) patients belonged to the VLNT and VLNT-BR groups, respectively. The groups were similar in terms of patient age (p = 0.766), BMI (p = 0.316), and duration of BCRL (p = 0.994). Verdye was used as the contrast agent for imaging in 9 out of 51 patients, whereas technetium was used in the remaining patients.

Volume difference between the donor and non-donor extremities

One patient had missing volume measurements on the lower extremities at the 3-month post-op visit. The mean volume difference between the donor and non-donor extremities at the pre-op visit was 48.1 ± 334.7 ml (range: −609.1-848.4 ml) and at the 12-month post-op was −70.7 ± 293.2 ml (range: -799.4-520.2 ml; Table 1 and Figure 2A). The total change in mean volume difference between pre-op and 12-month post-op visits was −22.6 ± 383.9 ml (range: −813.2- 860.2), 95% CI [−85.4-130.6], (p = 0.676; Figure 2B). The duration of BCRL significantly influenced the changes in lower extremity total volumes difference over the course of the one year OR 14.49, 95% CI (7.28-21.70) p< 0.001 (Table 2). There were five patients whose volume excess in the 12-month post-op visits was between 5% and 7.8%, and in six patients with volume excess between 1% and 4.9%.

Comparing the volumes between VLNT and VLNT-BR groups

At pre-op, the mean volume difference between the lower extremities in the VLNT group was 17.7 ± 372.2 ml (range: −568.3-848.3 ml) and in the VLNT-BR group, it was −111.3 ± 287.3 ml (range: −609.1-668.3 ml). At 12-month post-op, the mean volume difference in the VLNT group was 3.9 ± 223.6 ml (range: −378.2-520.2 ml) and in the VLNT-BR group, it was −142.3 ± 336.1 ml (range: −799.5-516.7 ml). When comparing the changes in mean volume differences for one year, there were no statistical differences between the groups: VLNT: −13.8 ± 329.5 ml and VLNT-BR: −31.0 ± 436.4 ml (p = 0.875; Figure 3).

Adverse events in flap harvest sites and lower extremities

Altogether, 65 donor-site adverse events were recorded in 41 (80.4%) patients during one-year follow-up. Overall, 14/51 (27.5%) patients experienced some adverse events during the treatment and hospital stay (Table 3), and 34/51 (66.7%) patients at any follow-up visit (Table 4). A total of 23 (56.1%) patients had only one event; nine (22.0%) patients had two, and seven (17.1%) patients had three or more adverse events. Altogether, 29/65 (44.6%) events were recorded in either the donor or non-donor lower extremities, 28/65 (43.1%) around flap harvest areas, and 8/65 (12.3%) in other areas or were not specified events (Figure 4). Logistic regression analysis did not reveal any patient-specific factors influencing the occurrence of adverse events (Table 5).

Table 1 Total mean volumes and volume differences between the donor and non-donor lower extremities at each study visit.

Study visits	Total volume of extremities (ml)		Volume difference range (%)	Mean difference [95% CI]	p-value*
	Donor extremity	Non-donor extremity			
Preoperative	7709.5 ± 1477.7	7757.5 ± 1569.5	−7.9 to 12.3%	−48.1 [−142.2 to 46.1]	0.310
3 months postoperative	7855.1 ± 1699.9	7878.0 ± 1717.9	−6.2% to 8.5%	−22.9 [−109.6 to 63.8]	0.598
6 months postoperative	7862.2 ± 1643.2	7917.7 ± 1657.3	−14.2% to 6.1%	−55.5 [−135.9 to 24.8]	0.171
12 months postoperative	7711.5 ± 1539.6	7782.2 ± 1561.2	−9.7% to 7.8%	−70.7 [−153.1 to 11.8]	0.091

Values are reported as mean ± standard deviation.
p-values of < 0.05 are considered as statistically significant.
* p-value donates the statistically difference between the donor and non-donor extremities in each study visits.

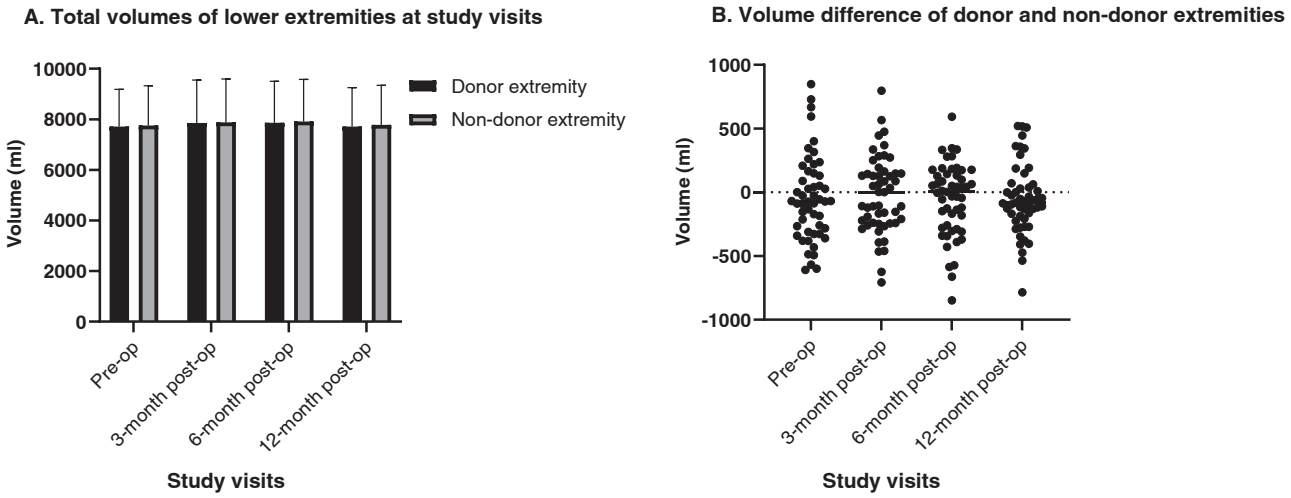

Figure 2 2A. Mean total volumes of lower extremities at each study visit did not exhibit any statistically significant differences between the donor and non-donor extremities ($p = 0.310$, $p = 0.598$, $p = 0.171$, and $p = 0.091$). 2B. The total mean volume difference among 51 patients at each study visit showed no statistically significant difference ($p = 0.733$) in mean volume difference in the lower extremities.

Table 2 Analysis of linear regression of the change of total volume difference of the lower extremities during one year with predictive factors.

Independent variable	ß (95% Cl)	p-value
Age (years)	−6.14 (−20.40 to 8.11)	0.390
BMI (kg/m^2) at pre-op	3.20 (−29.41 to 35.80)	0.845
BMI (kg/m^2) change for one year	28.78 (−65.04 to122.59)	0.540
Volume difference (ml) between lower extremities at pre-op	−0.77 (−1.02 to −0.53)	<0.001
Duration (months) of BCRL	14.49 (7.28 to 21.70)	<0.001
Volume difference (ml) in upper extremities at pre-op*	−0.122 (−0.387 to 0.143)	0.358
Volume difference (%) of upper extremities at pre-op*	−3.803 (−9.404 to 1.798)	0.179

ß = regression coefficient.
Cl = confidence interval.
* The volume difference in the upper extremities was measured without the compression garment.

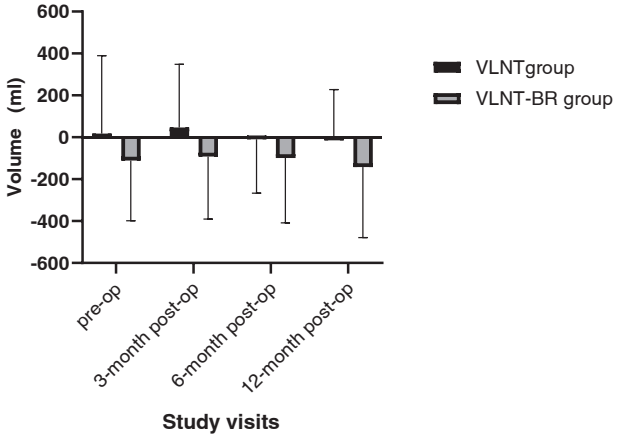

Figure 3 Mean volume difference between the lower extremities in the VLNT and VLNT-BR groups at each study visit showed no statistically significant differences between the groups (pre-op, ($p = 0.171$); 3-month post-op, ($p = 0.108$); 6-month post-op, ($p = 0.268$); and 12-month post-op, ($p = 0.075$)) or between study visits ($p = 0.941$). A negative value indicated a lower volume in the donor site extremities.

There were 6/65 (11.8%) seromas, 9/65 (17.7%) prolonged postoperative pain in the abdomen or flap harvest area, 4/65 (7.8%) hematoma/bleeding, 3/65 (5.9%) local wound infections, and 6/65 (11.8%) had other surgical wound health complications, such as wound edge necrosis and wound dehiscence. Four (7.8%) patients had pain in the lower extremity donor site, and six (11.8%) had pain in non-donor sites. Four (7.8%) patients had numbness/hypoesthesia in the lower extremity of the donor site, and another 4 (7.8%) had numbness/hypoesthesia in the non-donor extremity. Two patients (3.9%) had numbness/hypoesthesia in both the lower extremities. One patient (1.9%) reported lower extremities swelling without an increase in the volume difference. No secondary lymphedema was observed. Supplemental Table 1. lists all the recorded adverse events.

Serious adverse events (SAE)

Seven of the 51 patients (13.7%) had SAE. Among these, two were in the VLNT group, and five were in the VLNT-BR group ($p = 0.419$). One hematoma at the donor site in the groin area required reoperation (Grade 4). There were no life-

Table 3 All adverse events (AE and SEA) during treatment and hospital stay.

	Total (% of all 51 patients)	Groups		Classification of events			Events (n) recovered until 1-year post-op visit
		VLNT	VLNT-BR	Grade 1	Grade 2	Grade 3-4	
Total patients (n)	14 (27.5%)	7 (50%)	7 (50%)				
Number of all events (%)	16 (100%)	9 (56.3%)	7 (43.8%)	11 (68.8%)	4 (25%)	1 (6.3%)	n = 13 Recovered (81.3%) n = 3 Not recovered (18.8%)
Pain in the (non-donor) thigh/pain in the extremity	1	1			1		Recovered
Abdominal pain	2		2	2			n = 2 Recovered
Skin blister in (non-donor) tight	1		1	1			Recovered
Skin blister in (donor site) buttock	1	1		1			Recovered
Allergic rash in the support belt area/dermatic allergy	1		1	1			Recovered
Pain in operation area/procedural pain	2	1	1	1	1		n = 2 Recovered
Hematoma of the groin (flap donor site)	1	1				1 (Gr4)	Recovered
Yeast infection on skin/fungal skin infection	1	1		1			Recovered
Abdominal wound not healed, fluid under skin	1		1		1		Recovered
Numbness of the non-donor thigh/hypoesthesia	4	3	1	3	1		n = 2 Recovered n = 2 Not recovered
Nerve pain and hyperesthesia in the thigh	1	1		1			Not recovered

threatening consequences or deaths related to SAE (Grade 5; Table 6).

Management of AE and SAE

During the one-year follow-up, 54 (83.1%) of the 65 recorded AEs were either treated conservatively or spontaneously resolved (Tables 3 and 4). Two patients underwent repeated seroma aspirations owing to prolonged serous fluid secretion. For 5 out of 10 patients who experienced numbness/hypoesthesia in the thigh/lower extremities after surgery, sensation spontaneously returned during the one-year follow-up.

Comparison of the VLNT and VLNT-BR groups

There were 29/65 (44.6%) adverse events in the VLNT group and 36/65 (55.4%) in the VLNT-BR group (Tables 4 and 5). Procedural complications, including seromas, local wound infections, postoperative pain, and any wound dehiscence problems, occurred in 9/25 (36.0%) in VLNT and 16/26 (61.5%) in the VLNT-BR group, respectively, with no statistical difference between the groups ($p = 0.095$). Postoperative nerve damage, including numbness/sensory loss in the thighs, occurred in 7/25 (28.0%) patients in the VLNT group and 3/26 (11.5%) in the VLNT-BR group ($p = 0.173$; Figure 5).

Discussion

This prospective multicenter study examined the risk of donor-site morbidity in 51 patients with BCRL who underwent VLNT. The patient cohort was drawn from the Lymfactin® trials.[13] No secondary lymphedema was observed in the lower extremities of the donor site during the one-year follow-up period in this well-documented patient group. The most frequent postoperative complications included pain, wound healing problems, and seroma formation around the donor harvest area or the lower extremities. Notably, these adverse events were predominantly minor and did not lead to long-term morbidity. These findings confirm that the risk of developing secondary lymphedema in the donor site lower extremity is exceedingly low when groin VLNT procedures are performed in highly experienced surgical units and reverse lymphatic mapping techniques are employed.

The primary concern with groin VLNT is the risk of developing lower-extremity lymphedema owing to the removal of lymph nodes and vessels essential for draining fluid from the lower extremities. Understanding groin lymphatic anatomy is crucial in avoiding damage to the tissues that drain the lower extremities. Anatomical studies have revealed that most lymph nodes draining the lower extremities are medial to the femoral vessels and central inguinal areas.[7,19] Lymph nodes draining the supra-iliac region and lower abdominal walls are located lateral to the femoral artery. Only the lateral lymph nodes should be harvested, and the lymphatic flap should remain positioned above the inguinal ligament. In addition to these surgical

Table 4 All adverse events (AE and SEA) during one-year post-treatment among 51 patients.

	Total (% of all 51 patients)	Groups		Classification of events			Events (n) recovered until 1-year post-op visit
		VLNT	VLNT+BR	Grade 1	Grade 2	Grade 3	
Total patients (%)	34 (66.7%)	15 (44.1%)	19 (55.9%)				
Number of all adverse events	49	20 (40.8%)	29 (59.2%)	31 (63.3%)	12 (24.5%)	6 (12.2%)	n = 41 Recovered (83.7%) n = 8 Not recovered (16.3%)
Pain in donor site extremity	4	1	3	4			n = 4 Recovered
Pain in the non-donor extremity	4	2	2	4			n = 2 Recovered n = 2 Not recovered
Pain in both extremities or not mentioned which side	5	2	3	5			n = 3 Recovered n = 2 Not recovered
Unspecified pain in muscles or joints	6	2	4	5	1		n = 6 Recovered
Post-operative pain in the flap harvest area	7	3	4	3	4		n = 6 Recovered n = 1 Not recovered
Wound healing problem	5	1	4	1	2	2	n = 5 Recovered
Seroma	6	4	2	2	3	1	n = 5 Recovered n = 1 Not recovered
Hematoma/ bleeding	3	1	2	2	1		n = 3 Recovered
Postoperative infection	3		3			3	n = 3 Recovered
Numbness of donor site inner thigh cutaneous femoris symptoms	4	2	2	4			n = 2 Recovered n = 2 Not recovered
In the anterior part of both thighs, numbness, tenderness, and hyperesthesia	1	1		1			n = 1 Recovered
Vaginal bleeding	1	1			1		n = 1 Recovered

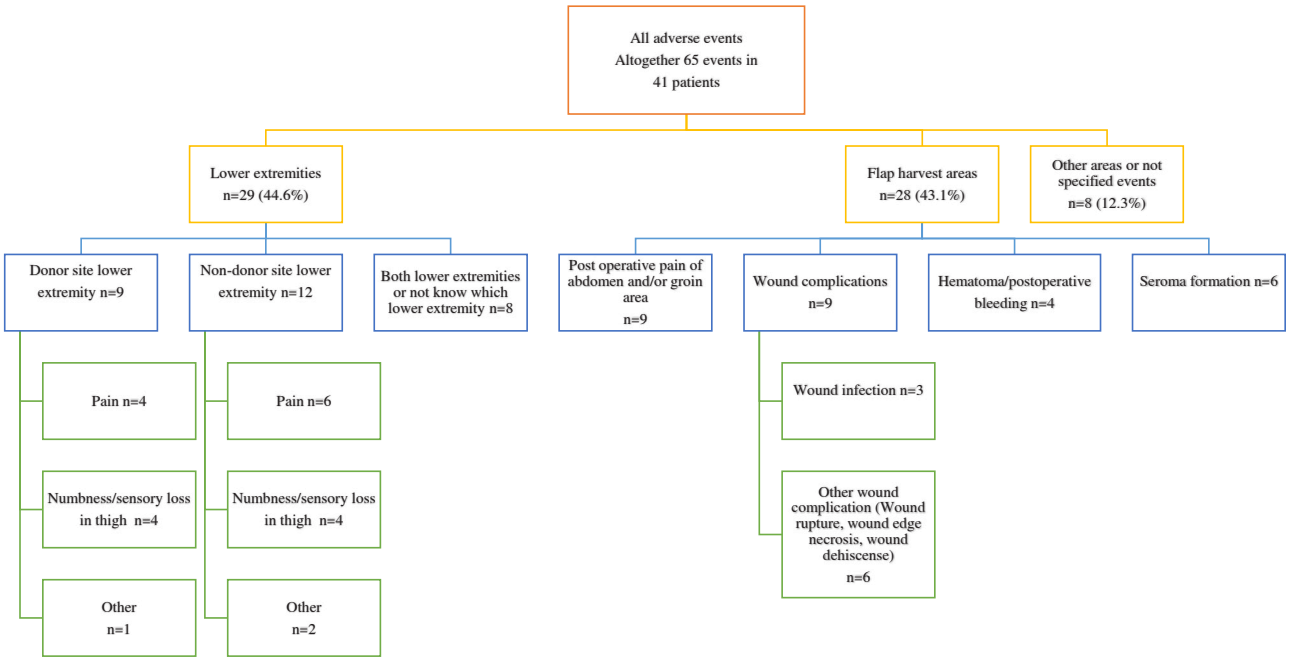

Figure 4 All adverse events (n = 65) were divided into three categories: lower extremities, flap harvest area, and all other areas.

techniques, reverse lymphatic mapping can further reduce the risk of secondary lymphedema.[12,20,21]

The groin is commonly selected for VLNT owing to well-studied anatomy, abundant lymph nodes, easy surgical access, and minimal hidden scarring.[7,11,19] The flap can be effectively used in combination with breast reconstruction.[3] For patients who do not require or are unsuitable for abdominal flap reconstruction, several alternative VLNT donor sites are available.[22,23] One option is the gastroepiploic VLNT flap (GE-VLNT), which involves harvesting the right gastroepiploic artery from the omentum using laparoscopy. The GE-VLNT flap has advantages, including the lack of risk of skin infection or secondary swelling at the donor site and adequate lymph node content.[6,24] However, its harvesting requires laparoscopic expertise. Other potential donor sites for lymphatic flaps include the neck (submental flap) and thoracic wall (supraclavicular flap and lateral thoracic lymph node flap).[25-27] Notably, when comparing the groin flap to the other options, there is limited clinical experience, particularly in the surgical treatment of BCRL.[28]

Diagnosing secondary lymphedema primarily relies on clinical features and measurement of volume differences between the extremities. As a standard, a volume excess of $>10\%$ is typically considered diagnostic for lymphedema.[16] In this study, we employed the Brorson method.[15] This specific method is non-invasive, easily conducted in an outpatient clinic, and repeatable, making it a practical choice for assessing lymphedema.

Previous studies have shown that secondary lymphedema after groin VLNT is rare.[9,28,29] Vignes et al. reported that only two of 14 patients developed it after groin VLNT treatment, but they did not use reverse lymphatic mapping.[10] Liu et al. used reverse lymphatic mapping in a cohort of 30 patients with BCRL who underwent VLNT treatment, and no patients developed secondary lymphedema.[30] In this study, the volumes of the lower extremities were meticulously measured before treatment and on three occasions after treatment. All potential clinical features that could indicate secondary lymphedema were carefully documented during each study visit. One year after treatment, the donor site volume was lower than the opposite extremity volume by -70.7 ± 293.1 ml. Importantly, there were no significant volume changes over the year and no patients exhibited a volume excess of $>10\%$ at the 12-month study visit, which would indicate secondary lymphedema.

Table 5 One-predictor logistic regression of adverse events of donor area and/or lower extremities with predictive factors.

Independent variable	OR (95% CI)	p-value
Age (years)	0.98 (0.89–1.08)	0.647
BMI (kg/m^2) in pre-op	0.95 (0.77–1.17))	0.605
BMI (kg/m^2) change during one year	0.99 (0.55–1.79)	0.976
Volume (ml) different between lower extremities at pre-op	1.00 (0.99–1.00)	0.290
Duration (months) of BRCL	1.02(0.97–1.08)	0.441
Surgical treatment (VLNT vs. VLNT-BR)	0.95 (0.24–3.80)	0.945

OR= Odds ratio.
CI= Confidence interval.

Table 6 All serious adverse (SEA) events (Grade 3-5) in 7 (13.7%) out of 51 patients.

	VLNT-group	VLNT+BR-group	Period	Reoperation	Required or prolonged hospitalization	Required extra visits to the hospital
Total	7 (13.7%)	2 (28.6%)	5 (71.4%)		6 (11.8%)	2 (3.9%)
Mean age, years ± SD	56.3 ± 4.7					
Patient 1	Hematoma of the groin (Flap donor area) X		Treatment and hospital stay	Reoperation due to hematoma in the groin flap site.	NO	
Patient 2	Abdominal wound dehiscence	X	Follow-up		YES	YES
Patient 3	Wound edge necrosis	X	Follow-up		YES	
Patient 4	Infected seroma at the donor site X		Follow-up		YES	
Patient 5	Wound infection on the abdomen	X	Follow-up		YES	
Patient 6	Wound infection on the abdomen	X	Follow-up		YES	YES
Patient 7	Infection in the donor groin area	X	Follow-up		YES	

Based on our research, the duration of BCRL significantly affects the volume difference in the lower extremities after one year. However, there was no statistically significant relationship between the severity of BCRL and volume changes in the donor extremities. Evidence suggests a genetic predisposition to lymphedema, with over 20 identified genes related to lymphangiogenesis, angiogenesis, inflammation, and intercellular communication.[31,32] Although we did not test the patients in our study for genetic predisposition to lymphedema, we cannot exclude this possibility.

Furthermore, systemic effects of lymphedema, such as increased capillary filtration, elevated collagen levels, and higher CD4 T cell counts, have been observed in non-lymphedema arms.[33] Additionally, patients with lymphedema show higher VEGF-C levels in plasma compared to patients with breast cancer without lymphedema.[34] Progressing lymphedema is often characterized by chronic inflammation, which can cause swelling. To summarize, we can only speculate whether long-lasting lymphedema may increase capillary filtration in the lower extremities, potentially causing minor swelling after the flap harvest. This susceptibility could be related to the duration of lymphedema, as inflammation related to swelling may increase over time. However, the observed increase in volume could be related to secondary changes (e.g., collagen production) increasing with lymphedema progression. All this highlights the need for meticulous dissection and lymphatic tissue conserving techniques when harvesting lymph node flaps regardless of donor site.

Secondary lymphedema at the donor site is less common than other postoperative complications. This study's cohort was part of a larger medical drug research trial with rigorous independent data monitoring, ensuring a meticulous recording of all potential adverse events. These adverse events were systematically collected and graded during the follow-up study visits for up to 12 months. Mostly, 64.6% adverse events were categorized as mild and only 9.2% were classified as severe. The most frequently encountered complications were postoperative pain in the flap harvest area (17.7%), followed by surgical wound complications (11.8%), seroma formation (11.8%), and postoperative hematoma/bleeding (7.8%). These findings are consistent with those of previous studies.[10,26,30,35] Interestingly, postoperative pain in the non-donor lower extremities was slightly more prevalent than that in the donor site extremities (11.7% vs. 7.8%). During groin VLNT flap harvesting, there is a possibility of injuring the branches of the lateral femoral cutaneous nerve, which can result in pain or numbness in the thigh of the donor site. This occurred in 7.8% of the patients in the current study. Notably, 7.8% of patients also reported numbness in the non-donor thigh site. This result suggests that groin VLNT does not increase the damage to the lateral femoral cutaneous nerve at the donor site compared with the non-donor site. Over 80% of adverse events had resolved one year after surgery, leaving patients free of long-term complications at the donor site or in the lower extremities.

We compared the adverse event rates between the VLNT and VLNT-BR groups and found that approximately 55% of all adverse events occurred in the VLNT-BR group. Hamdi et al. reported that combining VLNT with DIEP led to a significantly higher occurrence of seroma formation, wound problems, and donor-site pain/numbness.[9] In this cohort, 4/

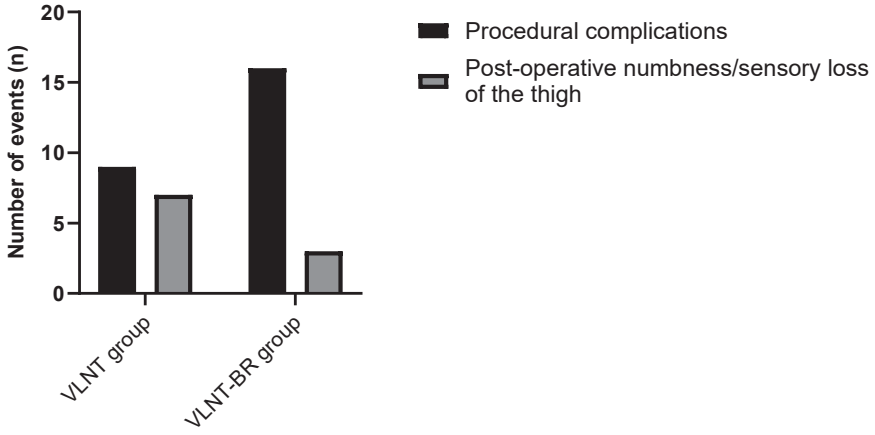

Figure 5 In groups, all procedural complications (seromas, local wound infections, postoperative pain, and any wound dehiscence problems) and postoperative numbness/sensory loss of the thigh. There were no significant differences between the groups regarding procedure complications ($p = 0.095$) or postoperative nerve damage ($p = 0.160$).

6 cases of seroma formation occurred in the VLNT group. Numbness or sensory loss around the lower extremities occurred more often in the VLNT group (28% vs. 11.5%), but the difference was not statistically significant.

This study has limitations that need to be acknowledged. Despite careful groin VLNT flap harvesting, there might be minimal injuries to the lymph vessels draining the lower extremities, which could cause subclinical secondary lymphedema. Postoperative lymphoscintigraphy could visualize even minor changes and damage to lymphatic flow.[11] Moreover, preoperative imaging, such as MRI or ICG lymphoscintigraphy, might have been helpful for flap design, but these imaging techniques were not included in the protocol of this study. Additionally, we did not compare our results with patients undergoing breast reconstruction without groin VLNT flap harvesting.

Conclusion

This study presents a large prospective cohort of groin VLNT flap procedures, with or without breast reconstruction. It shows a low risk of secondary lymphedema within one-year of surgery when performed by experienced teams employing perioperative reverse lymphatic mapping.

Ethical approval

This study was conducted in accordance with the ethical standards. The study protocols were approved by the Finnish Medical Agency (FIMEA), ethics committee of the Helsinki Hospital District, Swedish Medical Products Agency, regional ethics committee, and National Medical Board of Sweden. The study identifier numbers for the clinical trials are NCT02994771 and NCT03658967.

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Conflicts of interest

AS, SS, IK, JH, and PH have received honoraria for participating in advisory boards of Herantis Pharma Plc. (Espoo, Finland), which was responsible for Lymfactin® I and II trials management. All remaining authors have declared no conflicts of interest. The authors do not have financial disclosures to report.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bjps.2024.08.063.

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