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Abstract:

The treatment of breast cancer has seen great success in the recent decade. With longer survivorship, more attention is paid to function and aesthetics as integral components of treatment. However breast cancer related lymphedema (BCRL) remains a significant complication. Immediate lymphatic reconstruction is an emerging technique to reduce the risk of BCRL, Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) being the most widely used approach. Despite promising results, it is often difficult to find suitably sized recipient venules and perform the microanastomoses between mismatched vessels deep in the axilla. Moreover, high axillary venous pressure gradients and potential damage from radiotherapy may affect the long-term patency of the anastomoses. From an ergonomic point of view, performing lymphaticovenular anastomosis (LVA) in the deep axilla may be challenging for the microsurgeon. In response to these limitations, we modified the technique by moving the lymphatic reconstruction distally – terming it distally-based LYMPHA (dLYMPHA). 113 patients underwent mastectomy with axillary clearance (AC) in our institution from 2018 to 2021. 26 underwent subsequent dLYMPHA (Group 2), whereas 87 did not (Group 1). 17.2% (15 patients) and 3.84% (1 patient) developed BCRL in Group 1 and 2 respectively (p 0.018). Lymphatics and recipient venules suitable for anastomoses can be reliably found at in the distal upper limb with better size match. A distal modification achieves a more favorable lymphaticovenular pressure gradient, vessel match and ergonomics whilst ensuring a comparably low BCRL rate.

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The treatment of breast cancer has seen great success in the recent decade. With longer survivorship, more attention is paid to function and aesthetics as integral components of treatment. However, breast cancer related lymphedema (BCRL) remains a significant complication. Immediate lymphatic reconstruction is an emerging technique to reduce the risk of BCRL, Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) being the most widely used approach. Despite promising results, it is often difficult to find suitably sized recipient venules and perform the microanastomoses between mismatched vessels deep in the axilla. Moreover, high axillary venous pressure gradients and potential damage from radiotherapy may affect the long-term patency of the anastomoses. From an ergonomic point of view, performing lymphaticovenular anastomosis (LVA) in the deep axilla may be challenging for the microsurgeon. In response to these limitations, we modified the technique by moving the lymphatic reconstruction distally – terming it distally-based LYMPHA

(dLYMPHA). 113 patients underwent mastectomy with axillary clearance (AC) in our institution from 2018 to 2021. 26 underwent subsequent dLYMPHA (Group 2), whereas 87 did not (Group 1). 17.2% (15 patients) and 3.84% (1 patient) developed BCRL in Group 1 and 2 respectively (p 0.018). Lymphatics and recipient venules suitable for anastomoses can be reliably found at in the distal upper limb with better size match. A distal modification achieves a more favorable lymphaticovenular pressure gradient, vessel match and ergonomics whilst ensuring a comparably low BCRL rate.

Keywords: lymphedema, breast cancer, microsurgery, lymphovenous anastomosis

Introduction

Breast Cancer Related Lymphedema (BCRL) is a chronic, progressive disease that poses substantial psychological and economic burden[1]. According to a recent systematic review, 14.1% of patients who undergo axillary lymph node dissection (ALND) develop breast cancer related lymphedema (BCRL). Those who undergo ALND and adjuvant radiation have a 33.4% incidence of BCRL[2]. With great successes in the treatment of lower extremity lymphedema, reconstructive surgeons are now turning their attention to refining reconstructive techniques and improving quality of life in the treatment of BCRL. The use of prophylactic lymphaticovenular anastomosis (LVA) after axillary clearance has been implemented with the goal of reducing the risk of BCRL. Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) is the most widely used approach[3]. Despite promising results, concerns, it is often difficult to find suitably sized recipient venules and perform the microanastomoses between mismatched vessels deep in the axilla. Also, high axillary venous pressure gradients and potential damage from radiotherapy may affect the long-term patency of the anastomoses[4]. To mitigate against these risks, we modified the LYMPHA technique by shifting the immediate lymphatic reconstruction distally in the upper limb, terming it the distally-based LYMPHA technique (dLYMPHA).

Ideas

Methods

With Centralized Institutional Review Board approval (CIRB Ref: 2022/2619), we conducted a retrospective study on patients who had undergone ALND related to breast cancer in our institution from January 2018 to December 2021. Patients included in this study were women with breast cancer presenting with axillary metastasis requiring ALND. Informed consent was obtained from patients prior to publication of their clinical photos. As part of our institutional practice, dLYMPHA was offered to all patients requiring ALND during pre-operative counselling. The inclusion criteria for dLYMPHA were patients who require ALND related to breast cancer. The exclusion criteria were patients who did not require ALND, presence of systemic metastasis, or skin malignancy of the upper limbs. Patients with less than 6 months of follow-up were also excluded from this study, in order to exclude temporary swelling from post-operative changes. A total of 113 patients underwent ALND at our institution. 87 patients underwent ALND only (Group 1) and 26 patients underwent ALND with dLYMPHA (Group 2) (Table 1).

Limb circumference measurements are recorded by the same physiotherapist before surgery, at 3-monthly intervals post-operatively for the first year and at 6-monthly intervals thereafter. Each limb was measured at 4cm intervals and extrapolated to obtain an estimated volume of the limb. Lymphedema diagnosis is established when there is a 10% increase in volume and on lymphoscintigraphy more than 6-months after surgery.

Descriptive statistics were reported as the number (percentage or mean (SD)). Statistical analysis and logistical regression analysis was performed with STATA Ver. 17 (StataCorp, College station, Texas). Significance was set at 0.05.

Distally-based Lymphatic Preventative Healing Approach (dLYMPHA) Technique (Fig. 1-4)

Indocyanine green (ICG) lymphangiography is performed on table with Stryker SPY-PHI device (Stryker Corporation, Michigan) to map lymphatic channels. Recipient venules are identified using an infrared vein finder (Accuvein Inc, New York). To improve intraoperative visualisation of lymphatic channels, we routinely inject patent blue into the first 3 dorsal webspace of the hand. Incisions are planned based on the location of maximal confluence of the ICG and vein markings (Fig.3). The larger

lymphatic vessels in the upper limb run close to the cephalic and basilic veins [5]. To ensure adequate decompression of the both lymphatic systems, we will place a wrist incision on the radial wrist to capture the lymphatic vessels along the cephalic vein, and a bicipital groove incision to capture the lymphatics vessels along the basilic vein. Intraoperatively, lymphatics can be identified in the superficial subcutaneous tissue with uptake of patent blue dye. Venules that are of similar vessel diameter, close proximity and suitable direction of lie are selection.

LVAs are performed with 12-0 or 12-0s nylon sutures (Crownjun, Japan) in an end-to-end, end-to-side or multi-limbed fashion. Multiple LVAs are performed in each incision if possible. To reduce operative time, we adopt a dual team approach by performing dLYMPHA alongside the mastectomy or reconstructive team.

Results

All patients successfully underwent dLYMPHA in Group 2. The average number of LVA anastomoses performed in each limb was 3 (range 1 – 5 anastomoses). The median number of incisions were 2. The mean duration of surgery was 120 minutes. There were no statistical differences in demographics and patient characteristics between both groups (Table 1). In terms of surgical treatment, the patients in Group 2 (dLYMPHA intervention) had more lymph nodes removed on average than Group 1 (18.2 vs 14.2, $p=0.002$), suggesting a more aggressive ALND. In terms of oncological treatment, a higher proportion of patients in Group 2 (dLYMPHA intervention) underwent adjuvant chemotherapy (84.6% vs 50.6%, $p=0.0005$), suggesting that the patients in Group 2 may have higher proportion of aggressive cancers. The rest of the oncological treatment modalities such as adjuvant radiotherapy, neoadjuvant chemotherapy and neoadjuvant radiotherapy were not significantly different between the two groups. Post-operatively, the incidence of lymphedema was 17.2% (15 patients) and 3.84% (1 patient) in Group 1 and 2 respectively ($p=0.018$). The average follow-up period for all patients was 38.5 months.

The Numbers Needed to Treat (NNT) to prevent one case of lymphedema was calculated using the following formulas:

Discussion

According to the World Health Organisation (WHO) Global Breast Cancer Initiative, breast cancer is the most common cancer afflicting women. Advancements in early detection and treatment have increased life-expectancies with 5-year survival rates exceeding 90% in high-income countries. BCRL is the largest cancer survivorship burden for patients. It is associated with long-term impairments in Health-related quality of life (HRQoL) in the physical and psychosocial domains up to 10 years postoperatively[5]. Patients commonly experience impairments in upper limb mobility due to arm swelling, tightness, stiffness, and pain. The symptomatic sequelae negatively impact their body image, mental health, and limits engagement in social functions. The incidence of BCRL is 14.1% for patients who undergo ALND, and even higher at 33.4% for those who undergo adjuvant radiation[2]. The prevalence of BCRL will continue to increase in tandem with increasing survival rates. In a chronic incurable disease like BCRL, prevention is better than cure.

The surgical approach to nodal metastasis in breast cancer has undergone numerous evolutions with the aim of reducing morbidity and BCRL rates related to ALND. The advent of SLNB mitigated unnecessary ALND in clinically node-negative patients, and drastically reduced the rates of lymphedema in this group of patients[6]. The ACOSOG Z-0011 and EROTC AMAROS trials demonstrated that patients one or two metastatic sentinel nodes after SLNB, could safely avoid a completion ALND with the use of adjuvant radiotherapy[7,8]. However, in clinically node positive patients, surgical clearance of the axillary nodes remains the standard of care. Coupled with adjuvant radiation, these often resulted in lymphedema rates of up to 33%[9].

The concept of ILR was introduced by Boccardo in 2009 as the LYMPHA technique. It comprises of LVA between the axillary lymphatics and branches of the axillary vein. Long-term outcomes of the LYMPHA technique and demonstrated a 4.05% incidence of lymphedema over a 4 year follow up[10]. There is a growing number of evidence that have suggested the efficacy of this procedure. A meta-analysis by Johnson et al in 2019 showed that the pooled cumulative incidence of lymphedema was

significantly lower in patients who underwent ALND with LYMPHA (2.1% versus 14.1% $p=0.029$)[2]. Another meta-analysis by Hill et al in 2022 showed similar results favouring lymphedema reduction with LYMPHA (6.7 % of patients in the LYMPHA group versus 34% of patients in the control group developed lymphedema)[11]. However, there is little understanding of the oncologic safety of ILR after ALND, especially with the reconstruction done within a cancer field.

The basis for oncologic concern of ILR in the axilla stems from the theory that preserved lymphatics afferent to cancer-containing axillary lymph nodes are anastomosed to the systemic circulation via the LVAs. Remnant microscopic disease may be left behind along these afferent channels due to the proximity to axillary nodes. We are unable to reliably compare the oncologic safety between LYMPHA and dLYMPHA due to the paucity of long-term data [12,13], but by performing the LVAs distal to the axilla, we can safely avoid any theoretical iatrogenicity in cancer recurrence whilst providing similar rates of lymphedema incidence (3.84%, $p=0.018$).

Furthermore, the axilla is a target site for adjuvant radiotherapy and the LVA in LYMPHA is often directly irradiated. Even when it is not deliberately targeted, it receives substantial radiation dosages of up to 4961 cGy[14]. Impairment in lymphangiogenesis[15] and subsequent fibrosis caused by radiotherapy may affect the patency of any LVA performed. In the dLYMPHA technique, we prefer to perform at least two LVAs at separate sites on the bicipital groove and dorso-radial wrist crease. This puts the LVAs outside the zone of radiation, avoiding the possibility of future stenosis from radiation-related fibrosis. In addition, the large lymphatic vessels of the upper limb run along the cephalic and basilic venous systems. By performing LVAs to the dorso-radial wrist crease and bicipital groove, it allows the decompression of the cephalic and basilic related lymphatic vessels respectively. Thus, this allowed for efficient decompression of the upper limb below and above the elbow joint respectively, and anterolateral and anteromedial lymphangiosomes respectively [16].

There exist rich and variable lymphatic pathways along the anterior and posterior locations of the upper limb[17]. They all work to drain the upper limb into the axilla. Lymphatic channels are widely available and similar sized venules with lower venous pressures are typically adjacent and easy to locate. Better vessel match consequently translates to improved patency. In contrast to reports

utilising the LYMPHA technique, we did not encounter any situation where dLYMPHA was not suitable in the upper limb. Recognising similar shortcomings of the LYMPHA technique and advantages of moving the LVA distally, Orfahli et al proposed the use of a distally based LVA [18]. However, due to scheduling constraints, they were unable to coordinate the oncologic resection and lymphatic reconstruction into one event. We did not face these logistical constraints in our centre and were able to perform surgery concurrently with the breast resection or reconstruction, thereby reducing operative time. We routinely deploy two microscopes and two microsurgical teams, if necessary to allow the lymphatic and breast reconstruction to occur simultaneously (Fig. 4). To optimise space management between the lymphatic reconstructive and breast team, we perform the dLYMPHA with an arm board extension from the operating table. Additionally, the dLYMPHA technique is performed with the surgeon positioned perpendicularly to the arm, allowing for a more ergonomic posture, and allowing the participation of a surgical assistant seated opposite. In the classic LYMPHA technique, the surgeon would have to position himself diagonally oblique to the axilla to perform the LVA, obviating the possibility of having a surgical assistant.

In terms of potential risk factors, obesity has been associated with increased risks of lymphedema [20]. However, obesity is itself not a causative factor for lymphedema unless it is at the extreme level where the BMI is more than 40. In our cohort, the mean BMI for both treatment (dLYMPHA) and non-treatment groups are similar at 25.2 and 24.0 respectively with no statistically significant differences ($p=0.296$). This showed that lymphedema can occur in our patients even when they are at normal or near-normal BMI of 25. In addition, even when performed in normal BMI patients, dLYMPHA can reduce the risk of BCRL. Therefore, our group is of the opinion that high BMI should not be used as an inclusion criterion for dLYMPHA, and neither is normal BMI an exclusion criterion for dLYMPHA.

Another potential risk factor for the development for BCRL is the number of lymph nodes retrieved and the aggressiveness of breast disease. In our study, the number of lymph nodes removed was higher in the dLYMPHA group (18.2 vs 14.2, $p=0.002$). Despite this, the rate of lymphedema was still lower in the dLYMPHA group. In addition, there was a higher percentage of patients undergoing adjuvant chemotherapy in the dLYMPHA group (84.6% vs 50.6%, $p=0.0005$). This highlights a few points that strongly supports the dLYMPHA technique. Firstly, when the resecting surgeon knows that

there will be lymphatic intervention, they can confidently perform a more thorough ALND to achieve R0 margins, and not be adversely influenced by the fear of causing BCRL. Secondly, dLYMPHA demonstrates its effectiveness even in the presence of a more extensive axillary lymphatic disruption. Thirdly, despite the presence of a more aggressive disease that requires adjuvant chemotherapy, dLYMPHA could still reduce the risk of BRCL.

In our cohort, the numbers needed to treat to prevent 1 case of lymphedema was 7 patients. This was similar in the use of low-dose low molecular weight heparin to prevent deep vein thrombosis[19]. This suggests that the dLYMPHA technique has the good risk benefit/risk ratio in the prevention of BCRL. Though better size match can be achieved between lymphatics and venules in the upper limb, the biggest challenge of the dLYMPHA technique is finding suitable venules that are of close proximity and the technical difficulty of performing the anastomoses. In our series, there were no prior pathological dilatation of the lymphatic vessels from lymphedema, and due to their distal locations, the diameter of the lymphatic vessels only ranged from 0.15mm to 0.30mm. Unlike the lymphatic channels of secondary lymphedema that are already dilated due to lymphatic obstruction, these lymphatic channels are at normopressure, transparent and difficult to dilate with forceps. Hence, they can pose significant technical difficulties. In order to ensure good long-term outcomes, any potential risk of anastomotic failure must be prevented. Selection of anastomotic locations, best size match and mastery of supermicrosurgical techniques are will help to improve patency and success rates[20]. Another disadvantage of the dLYMPHA technique were the presence of additional scars distal to the axilla. We limit the size of our incisions to 2cm and preferentially placed them on the medial bicipital groove and on the distal wrist, where they can be hidden by sleeves and watch straps respectively (Fig 3).

Conclusion

Distally-based Lymphatic Preventative Healing Approach (dLYMPHA) demonstrated good potential in primary prevention of breast cancer related lymphedema and is an alternative to its predecessor, the LYMPHA technique. Further research is required to establish the long-term results and oncological safety of both the LYMPHA and dLYMPHA technique.

Conflict of Interest Declaration

There are no sources of funding for this work. The authors have no financial interests or financial disclosures to make. The authors have no conflicts of interest or commercial associations to declare.

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Table 1 Demographics and background of patients in the study, with ALND only (Group 1) versus ALND with dLYMPHA (Group 2). * denotes a statistically significant result.

	GROUP 1 (N=87)	GROUP 2 (N=26)	
DEMOGRAPHICS			
MEAN AGE (YRS)	59 (29 – 97) (SD:13.0)	54 (35 – 79) (SD:11.2)	p= 0.0784
BMI	24.0 (15.1 – 43.3) (SD: 4.82)	25.2 (18.7 – 33.8) (SD:4.12)	p= 0.193
SURGICAL CHARACTERISTICS			
SKIN SPARING	60 (69.0)	19 (73.1)	p=0.949
MASTECTOMY (%)			
NIPPLE SPARING	10 (11.5)	4 (15.4)	p=0.953
MASTECTOMY (%)			
LUMPECTOMY (%)	15 (17.2)	1 (3.84)	p=0.547

CHEST	WALL	2 (2.30)	2 (7.69)	p=0.400
RESECTION (%)				
LYMPH	NODES	14.2 (1 – 47)	18.2 (1 – 38)	p=0.002*
RETRIEVED				
METASTATIC	LYMPH	4.01 (0 – 36)	2.65 (0 – 20)	p= 0.161
NODES				
ONCOLOGIC				
TREATMENT				
CHARACTERISTICS				
NEOADJUVANT		37 (42.5%)	12 (46.2%)	p=0.746
CHEMOTHERAPY (%)				
NEOADJUVANT		0	0	NA
RADIOTHERAPY (%)				
ADJUVANT		44 (50.6%)	22 (84.6%)	p=0.0005*
CHEMOTHERAPY (%)				
ADJUVANT		57 (65.5%)	19 (73.1%)	p=0.476
RADIOTHERAPY (%)				

Fig 1. End to End LVA showing good flow of patent blue flowing across anastomosis. (Black arrow – vein, White arrowhead – lymphatic vessel)

Fig 2. An LVA formed by anastomosing 2 lymphatic channels (white arrowhead) to 1 venule (black arrow), showing good flow of patent blue across anastomosis.

Fig 3. Left arm showing incisions (black arrows) near medial upper arm and over radial wrist.

Fig 4. Intraoperative positioning for microscopes to allow simultaneous dLYMPHA and breast flap inset.





