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Breast cancer treatment-related lymphedema (BCRL): An overview of the literature and updates in microsurgery reconstructions

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ABSTRACT

Breast cancer is the most common cancer in Dharmais hospital. The treatment can give rise to breast cancer treatment-related lymphedema (BCRL) that will cause significant morbidities. Based on author's (BB) patient series in Dharmais hospital, BCRL occurred in 27.7% after axillary lymph nodes dissection (ALND). The development of diagnostic modalities as well as lymphatic microsurgery have become promising instruments for lymphedema treatment. To date, modern approach of lymphedema care and surgical intervention have not been recognized and established in Indonesia. A literature review in this field is needed to overcome our limitation in BRCL or lymphedema management.

Background

Breast cancer is the most frequent cancer in Indonesia which contributes to the highest incidence rate among other cancer in 2018 [1]. If compared with developed countries, the majority of our patients that come to hospitals are in advanced stages [2,3]. Breast cancer treatment for this group of patients, such as axillary lymph nodes dissection (ALND) can lead to development of breast cancer treatment-related lymphedema (BCRL) [4]. Although sentinel node biopsy (SNB) has just been applied in Indonesia for early stage, our previous study found that 53% of metastases were also occurred in non-sentinel nodes (NSN) after positive sentinel nodes (SN) biopsy [5]. Based on author's (BB) 65 patient series in Dharmais hospital, BCRL occurred in 27.7% after ALND with or without adjuvant radiation. For these reasons, ALND is still routinely being performed by our surgical oncologists and it could risk patients for developing BCRL.

So far, the modern lymphedema treatments have not been applied in Indonesia. Since BRCL can diminished the quality of life after breast cancer treatment, it is important for us to learn how to treat the condition properly. A literature review is needed to overcome our limitation in BRCL or lymphedema management. The purpose of this review was to discuss the state-of-the art of lymphedema basic knowledge and BRCL management, focusing on the development of microsurgery techniques as surgical interventions.

Incidence and risk factors

Lymphedema is defined as a protein-rich fluid accumulation in the interstitial tissue because of lymphatic system's disability to transport lymph fluid from the affected sites to the circulatory system [6]. In breast cancer treatment-related lymphedema (BCRL), axillary lymph nodes dissection (ALND), sentinel node biopsy (SNB), and radiation therapy disrupt lymphatic flow, resulting in soft tissue's protein-fluid retention and subsequent progressive development of fatty tissue and fibrosis in the arm [4,7]. The negative impacts on quality of life have been demonstrated to affect both physical and psychological aspect of patients. Diminished arm strength, range of motion, pain, heaviness, anxiety and frustration are well documented in BCRL patients [6]. Reduced patient's productivity and higher cost of treatment are another important socioeconomic burden issue which must be addressed appropriately in the future to overcome this distressing condition [8,9].

Several studies have reported on the incidence of BCRL which is ranged from 9% to 42%. This variation could be influenced by several factors, such as, differences in measurement methods (patients' self-reported symptoms, objective assessment, single or multiple methods), length of follow up, and the types of study design [4,11–15]. Risk factors have been identified which comprise of

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ALND, mastectomy, high body-mass index (BMI), radiotherapy, chemotherapy, reducing physical activity, and life style (blood pressure, hand use, self-care treatment, lymphedema education) [4,10–12,15].

Among the risk factors, a recent meta-analysis has acknowledged ALND, mastectomy, a higher number of axillary lymph nodes (ALN) dissected, and a high BMI as significant risk factors that were supported by a strong level of evidence. Whereas positive axillary lymph nodes metastasis, adjuvant radiotherapy or chemotherapy, and not performing regular physical activity were proven by a moderate level of evidence [11]. The number of axillary lymph nodes taken from ALND has a significant contribution as well. Dissecting more than 10 ALN can increased BCRL up to 2.81 times higher compare less than 10 ALN [16]. Interestingly, Killbreath et al. [12] reported 18,2% patients had arm lymphedema even only when the ALN were taken more than 5. These studies underline that axilla surgery is a significant factor for BRCL development. But, the nature of multimodality treatment in breast cancer can cause the emergence of the disease. All breast cancer treatment-related factors could contribute to it, which makes a surgery is not a single factor for BCRL [4].

Anatomy and physiology of the lymphatic system

The lymphatic system plays an important role to the circulatory and immune systems [17–19]. Ninety percent of fluid in the interstitial tissue drains back to systemic circulation via venous system and 10% enters back by means of lymphatic system [17]. Lymph nodes will activate immunologic reactions when any pathogens is transported through lymphatic vessels [17,18].

Anatomically, the lymphatic vessel structure is divided into capillary, pre-collector, and collecting vessel [18]. The lymph capillaries are located beneath the epidermis with the diameter between 20 and 70 μm. They do not have valves and only structured by a single layer of lymphatic endothelial cells (LEC). The capillary vessels are highly permeable because the connections between LEC by fibrous structured called an anchoring filament are loose and in overlapping pattern. Increasing pressure in interstitial tissue opens the endothelial cells outward allowing the interstitial fluid entering the lumen. After entering the capillaries, the lymph fluid will drain to pre-collector vessels (70 and 150 μm in diameter). Pre-collectors have valves which regulate unidirectional flow of lymph fluids. They are located in the deeper layer of dermis, converge to form larger vessels and running vertically in subcutaneous tissue to connect with collector vessels. The diameter of collector vessels is between 150 and 500 μm, running horizontally in the subcutaneous tissue and it has valves to maintain unidirectional flow. Fig. 1 describes the scheme of lymphatic system. The wall is made by three layers: LEC, smooth muscle cells (SMC), and collagen fibers. Lymphatic vessels do not have a centralized pumping system like on arterial and venous system and lymphatic fluid movements are stimulated by intrinsic and extrinsic factors. Lymphangion as an electrical pacemaker which is bounded by valves and LEC, will initiate the intrinsic pulsation of lymph fluid's flow. Extrinsic factors such as skeletal muscles contraction, massage, increased hydrostatic pressure by postural gravity can also give influence to rate of lymphatic flow [17–19]. The lymph collectors are categorized into superficial and deep vessels in their relation with the deep

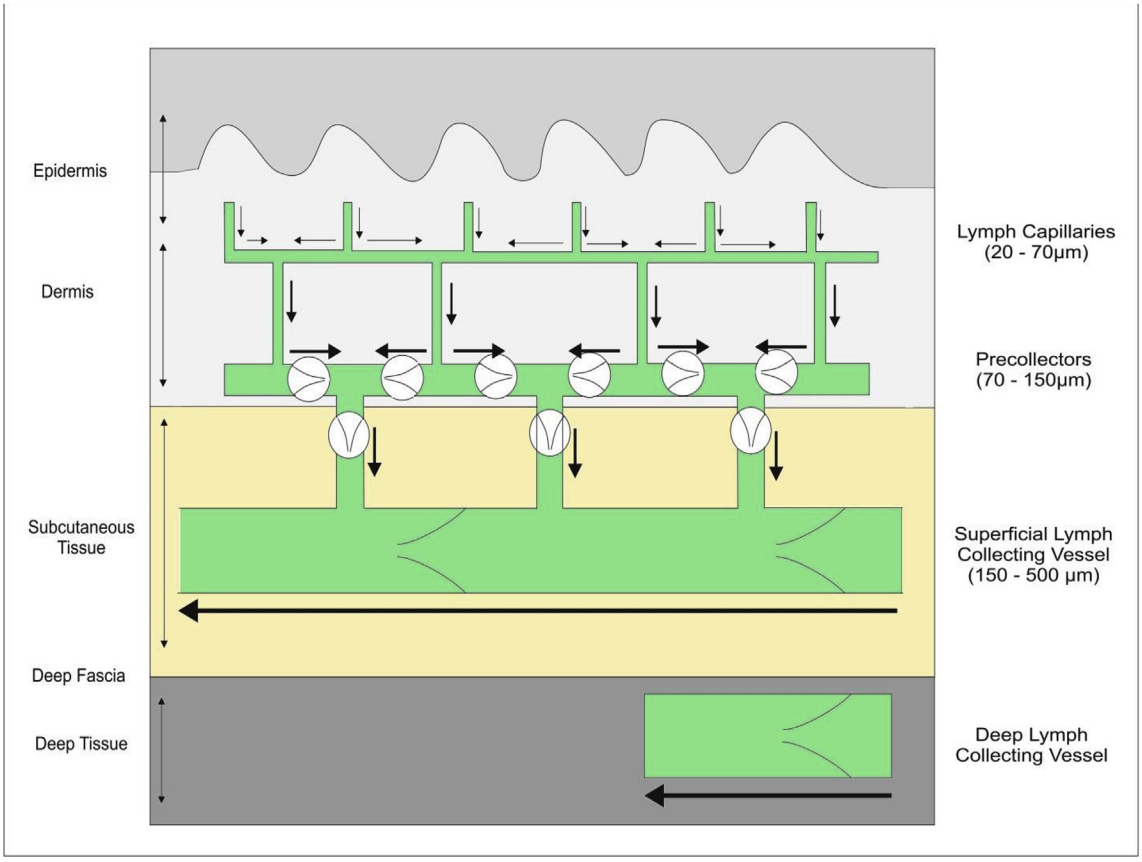

Fig. 1. Anatomy of the lymphatic system. Lymph flows from the lymphatic capillaries in the dermis to the precollecting lymphatic vessels, and to the collecting lymphatic vessels; going proximally and finally flowing into venous circulation at the venous angle through lymph node filtration.

fascia. Normally, there is no connection between the superficial and deep collectors but unusual connection between superficial and deep lymphatic system can be found after axillary dissection [18,20].

The lymphatic vessels will eventually drain to the lymph nodes before connecting to the vein. The fluid enter lymph nodes by the afferent vessels within the subscapular sinus and exit through the efferent vessels. More importantly, lymph nodes may contain lymphaticovenous communications (LVC) which can drain lymph fluid from surrounding tissue into the node and to the intranodal vein [19]. LVC is an important anatomical structure for the physiology of vascularized lymph nodes transplant (VLNT) [21].

The lymph collecting vessels of the upper extremity run axially from fingers to the dorsal part of the hands and making a direction toward the elbow, running to the anteromedial area of the upper arm and connected to axillary lymph nodes in the lateral region. A direct alternative route to supraclavicular nodes could be identified. These lymphatic vessels running in the lateral side of upper arm, parallel to cephalic vein and drained to supraclavicular nodes [18].

Pathophysiology of BCRL

The lymphatic system blockage will be followed by congestion of lymphatic flows. The increasing internal pressure at lymphatic vessel collectors will be distributed to capillaries and when it exceeds interstitial pressure, the contraction of filaments will open the channels between LEC and lead to lymphatic fluid extravasation to interstitial tissue. Lymphatic valves damage will occur if prolonged intraluminal hypertension is not resolved and lymph fluid backflow in the lymphatic vessel collectors will start to develop. Under this circumstances, SMC damage will eventually aggravate lymph fluid transport capacity. The fluid accumulation in the interstitial tissue can generate fat deposition that will lead to adipose tissue hypertrophy and along with impaired lymphatic immune system, dermato-lymphangio-adenitis (DLA) can finally occur [22,23].

It has been reported that the anatomical changes are related with the lymphedema severity [24,58]. The pathologic changes in the collecting lymphatic vessels were characterized as lymphosclerosis; with progression of lymphedema, lymphatic vessels become sclerotic from s0 to s1, s2, and finally to s3. “s0” lymphatic vessels are characterized as translucent appearance with histologically normal structures of the vessel wall. “s1” and “s2” lymphatic vessels are characterized as white appearance with thickened vessel wall because of hypertrophic tunica media (lymphosclerosis); “s1” vessels have thick wall but are expandable, whereas “s2” vessels have thicker wall and are not expandable because of accumulation of collagen fiber in the tunica media. “s3” lymphatic vessels are characterized as “pinhole” or “invisible” lumen vessel because of severe lymphosclerotic changes. In the normal condition, lymph flows from the lymphatic capillaries to the pre-collecting lymphatic vessels, and to the collecting lymphatic vessels normogradely with the normal structure of the LEC, the SMC, and the collagen fibers of the collecting lymphatic vessels. After lymph flow obstruction by surgical or radiological interventions, dilation of the collecting vessels lumen, LEC flattening, weaken intercellular attachment, transformation of contractile SMC into synthetic SMC which promotes collagen fibers production, and exposure of collagen fibers into the lumen were identified. The transformed synthetic SMC in the medial layer were migrated beneath LEC. The collagen fibers that was produced by synthetic SMC, made the contractility function of contractile SMC in the medial layers decreased. With progression of lymphedema, intercellular attachment between LECs is becoming lost, which worsens lymph fluid extravasation to interstitial tissue, collagen fibers domination that eventually narrowed or occluded the lumen and aggravated lymphedema because of total function loss of collector vessels.

Several studies have been done evaluating the lymphatic system changes after lymph nodes dissection. In mice, dermal backflow (DB) and collateral lymphatic pathways were developed following a lymph nodes dissection. The origin of these collateral pathways could be from the pre-existing ruptured afferent and efferent vessels or newly formed vessels. Although these new collateral vessels were created, their function might be disturbed by tissue remodeling and fibrotic changes. Radiation therapy after ALND could worsen the fibrotic changes [25]. Suami et al. [20] identified several unusual lymphatic pathways after ALND in a human cadaver study. He described, that following ALND there were types of lymphatic communications. Type A: backflow of lymphatic fluid to pre-collector vessels. Type B: the opening of lymphatic channels between superficial collecting vessels. Type C: the opening of lymphatic channel between superficial and deep collecting vessels. Type D: atrophic changes and disappearance of lymphatic vessels at the upper proximal arm. Type E: the possibility of lymphovenous shunts formation.

The existence of perforating lymphatic vessels could also explain another functional collateral lymphatic drainage after lymphatic obstructions. These perforating vessels have been identified in a mouse model and a human cadaveric study on post ALND. The perforating lymphatic vessel is another type of a lymphatic vessel which is located in subcutaneous tissue and run to join the deep lymphatic system, but it is not a communicating vessel between superficial and deep lymphatic system. These vessels could present in normal condition, but would only be functionally activated to create collateral pathways when there are lymphatic obstructions. Further studies are needed to clearly describe the role of lymphatic perforating vessel in lymphedema pathophysiology [18,20,26].

There is an evidence that the newly formed lymphatic vessels would be interfered on its function capacity due to fibrosis mechanism after ALND and or radiation. It is common to observe lymphedema presentation long time after surgery or radiation. Regeneration of disrupted lymphatic pathways will occur after ALND without lymphedema signs, but later the swelling can become evidence in any time after additional exposure to inflammation. The reformed lymphatic vessels that should prevent lymphedema appearance would suffer decreasing functions because of worsening fibrosis state since fibrosis has been identified as a key factor to regulate lymphangiogenesis [27,28].

Clinical manifestation and measurement

In general, lymphedema is classified into primary and secondary onset. Primary lymphedema is a rare condition and more than 20 gene mutations have been identified to cause undeveloped and malfunction in lymphatic system. Based on age of onset, it is divided into: congenital (after birth), praecox (puberty), tarda (after puberty or 35 years old). Secondary lymphedema is more common than primary lymphedema and caused by damage or obstruction of normal lymphatic system. Infections, trauma, surgery, morbid obesity, malignancy, and adjuvant cancer therapy can create secondary lymphedema.

Clinical symptoms of heaviness sensation and extremity discomfort at the end of the day can manifest on the affected extremities. Pitting edema will develop along with disease progression and peau d'orange becomes visible. When lymphedema worsens, skin thickening and fibrosis emerge. Skin over the affected sites showing hyperkeratotic changes and susceptible to ulceration and recurrent cellulitis. In a rare condition, prolonged lymphedema

can lead to angiosarcoma, a malignant neoplasm with aggressive behavior. Chronic venous insufficiency, cardiac or renal failure, lipedema (chronic progression disorder of adipose tissue), hypoalbuminemia, and drug-induced edema must be ruled out because of their similarities to lymphedema [29].

International Society of Lymphology (ISL) lymphedema staging system is commonly used for classification. Stage 0 or (1a): latent or subclinical condition. No evidence of swelling despite impaired lymph transport, subtle alteration in tissue fluid/composition, and changes in subjective symptoms. Stage I: fluid accumulation which subsides with limb elevation. Pitting edema may occur. Stage II: pitting edema manifestation and irreversible tissue swelling by limb elevation. In late stage II, pitting edema is not present and fibrosis develop. Stage III: lymphostatic elephantiasis with trophic skin changes such as acanthosis, alteration in skin character and thickness, further fat deposition and fibrosis, and warty overgrowth [30].

Numerous clinical measurements have been studied for lymphedema diagnosis. Recent systematic review has recommended bioimpedance spectroscopy (BIS), water volumetry, tape measurement, and perometry for lymphedema measurement because of their good reliability and validity. Based on feasibility in clinical practice, water volumetry and tape measurement are the preference, especially for upper extremity lymphedema. Tape measurement has the advantage for patients' self-management measurement, so they can evaluate lymphedema by themselves or by their families [31]. The cut-off point of lymphedema for water volumetry is $\geq$ 200 ml, and $\geq$2 cm for tape measurement [31,32]. Ideally, tape measurement must be calculated in volume. Truncated cone, disk, rectangle, trapezoidal formula can be used to calculate the volume [31].

Although volume measurement is the most objective methods for lymphedema diagnosis, it has several limitations. First, in bilateral lymphedema, the normal extremity cannot be used as a reference test. Second, physical body types will affect volume of the extremity. So, it is difficult to compare an objective volume between different individual's body type. To address this issue, Yamamoto et al. [33–35] has developed the upper extremity lymphedema (UEL) index as a simple and objective method which calculates BMI for body type correction (Fig. 2). The index is calculated by taking the sum of the square circumference in 5 areas of an upper extremity and dividing it by BMI. The calculated areas are the circumference at olecranon, 5 cm above and below olecranon, wrist joint, and dorsal of the hand. The index increased along with the increasing lymphedema stages. It has also been shown that results not to be affected by the increasing BMI as conventional arm volumetry has. Considering its simplicity and objectivity, UEL index will be useful in clinical practice application.

Imaging modalities technologies has supported lymphedema diagnosis, treatment, and follow up. Professor John Kinmoth introduced lymphography technique by cannulating lympathic vessels under microscope and infusing oil-soluble iodinated contrast medium. Lymphatic vessels and lymph nodes can be visualized by his methods, but because of its technical difficulty the technique is rarely used nowadays. Lymphoscintigraphy (LG) is considered as the goal standard for diagnosis. The severity of lymphedema and post-therapeutic outcome can be assessed. It is based on the transport of radiolabeled material by lymphatic system. It provides qualitative and quantitative evaluation. Qualitative assessment includes: the presence and caliber of lymphatic vessels, lymph nodes, collateral networks, and delay in radionuclide uptake. Radionuclide transit time, as defined by uptake and clearance time from the site of injection and clearance time from the limb, can be quantitatively assessed. However, lack of standard examination protocols, a long waiting examination time for the patients, and lower accuracy to detect early stage compared to fluorescence imaging make up its limitation.

Computed tomography (CT) and magnetic resonance imaging (MRI) scans visualize soft tissue. Skin, subcutaneous tissue, interstitial fluid, and muscle changes can be demonstrated and also the number and size of lymph nodes. Magnetic resonance lymphography (MRL) describes detailed anatomical and functional information of superficial and deep lymphatic system, as well as lymph nodes. Indocyanine green (ICG) lymphography has enable to better visualize lymphatic system. It allows direct and real-time assessment of anatomy and functional superficial lymphatic vessels, as well as lymph nodes [30,36]. ICG lymphography evaluation is classified into linear and DB pattern. Linear pattern is consistent with normally functional superficial lymphatic collectors. Dermal backflow pattern shows nonlinear image and further classified into splash, stardust, and diffuse pattern. With the progression of lymphedema, ICG lymphography image will change from linear to splash, stardust, and finally into diffuse pattern (Fig. 3). Based on DB pattern, arm dermal backflow (ADB) stage was made to assess the severity of UEL (Fig. 4). Stage 0: no lymphedema nor DB pattern is evidenced, stage I: splash pattern around the axilla, stage II: stardust pattern limited between axilla and olecranon, stage III: stardust pattern exciding olecranon, stage IV: stardust pattern throughout the limb, stage V: diffuse and stardust pattern throughout the limb [37–39]. ICG lymphography is more sensitive

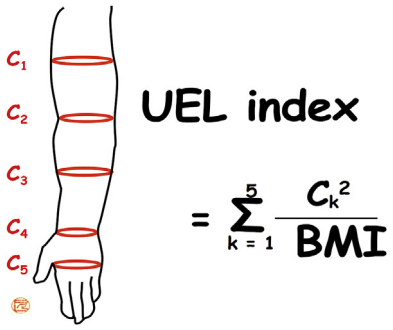

Fig. 2. Upper extremity lymphedema (UEL) index calculation. The arm is measured to obtain circumferences (cm) at the olecranon (C_2), 5 cm above and below the olecranon (C_1 and C_3), the wrist (C_4), and the dorsum of the hand (C_5). The UEL index is calculated by taking the sum of the squares of the circumference in C_1-C_5 and dividing it by body mass index (BMI).

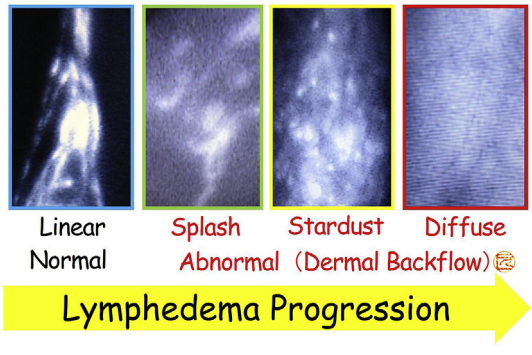

Fig. 3. Indocyanine green (ICG) lymphography examination and lymphedema progression. ICG lymphography evaluation is classified into linear and dermal backflow (DB) patterns. Linear pattern is normally functional superficial lymphatic vessels, while DB patterns indicate lymphedema. With the progression of lymphedema, ICG lymphography image will change from linear to splash, stardust, and finally into diffuse pattern.

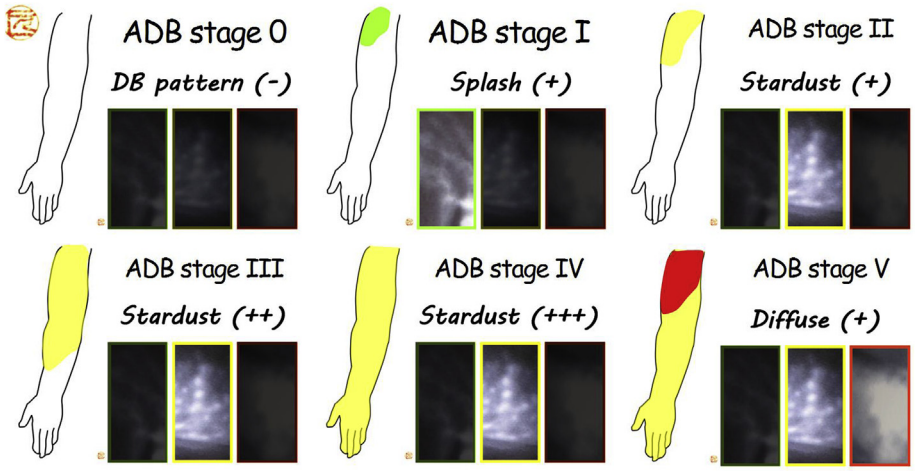

Fig. 4. Arm dermal backflow (ADB) stage. Based on dermal backflow (DB) pattern, ADB stage is made to assess the severity of UEL. Stage 0: no lymphedema nor DB pattern is evidenced, stage I: splash pattern around the axilla, stage II: stardust pattern limited between axilla and olecranon, stage III: stardust pattern exciding olecranon, stage IV: stardust pattern throughout the limb, stage V: diffuse and stardust pattern throughout the limb.

to detect early stage of lymphedema compare to LSG [40] but the ability to detect lymphatic channels in only a depth of 2 cm making its limitation [39]. Based on these findings, combination of LSG, ICG lymphography, and MRL are useful tools for lymphedema diagnosis.

Microsurgical treatment

Surgical approach to lymphedema can be classified into ablative and physiologic surgeries. Charles' procedure has been the most well-known procedure in ablative approach. Debulking surgery removes all skin and subcutaneous tissue in the lymphedematous area above the deep fascia and skin grafted the raw surface. Sistrunk and Thompson used the ablative concept in the upper arm with modifications to connect superficial to deep lymphatic system. Considering the effectiveness and morbidities, these procedure are no longer considered as options, unless in extreme cases [41]. Liposuction is also considered as an ablative procedure but it can be used in several conditions [41,42].

Physiologic surgeries use the concept of restoration of lymphatic drainage through bypasses into lymphatic system, venous system or creating new lymphatic pathways by lymphangiogenesis. Tissues with abundant lymphatic vessels such as omentum, skin, and musculocutaneous as pedicles flap have been used for lymphedema. Lymphaticolymphatic bypass using healthy lymphatic channels from medial thigh or vein interposition graft have been reported as a part of physiologic surgeries. All these procedures are not widely used because of the morbidities and not showing reliable results. With the advancement of microsurgery and supermicrosurgery techniques, the widely accepted lymphedema surgical treatment are lymphaticovenular (LVA) anastomosis and (VLNT) [41,43].

Lymphaticovenular anastomosis (LVA)

Laine's report on lympaticovenous anastomosis in rats was followed by Yamada's experimental study in dogs and subsequently in a lymphedema patients. His procedure was done using a microsurgical technique, comparing the patency of end to end and end to side anastomosis of lymphatic vessels to the saphenous vein. In 1 patient, he reported a circumferential decrease of lower extremity about 2 until 8 cm after 3 months of follow up [44]. O'Brien's study became a breakthrough in lymphedema microsurgery reconstruction. The proximal end of lymphatic vessels were anastomosed to a large cutaneous vein. In his 22 UEL patients with an average follow up of 11 month, 55% patients showed more than 10% reduction of excess volume but it was less effective in lower extremity lymphedema (LEL). The observed venous backflow into lymphatics due to high pressure of cutaneous veins, could be a contributing factor for the ineffectiveness of the technique [45,46]. Supermicrosurgery technique introduced by Koshima has led to a better LVA, which enable to perform intima-to-intima anastomosis between lymphatic vessels and subdermal venules less than 0.8 mm in size. The lower pressure from venular system is expected to reduce venous backflow, thus lowering the risk of thrombosis and increasing the successful of lymphatic drainage [46]. LVA is a minimally invasive procedure which can be done under local anesthesia with few centimeter skin incisions [47].

There are 2 types of lympho-venous shunt surgeries, lymphaticovenous implantation and LVA. In lymphovenous implantation, lymphatic vessels are inserted into a vein with a microsurgery technique whereas in LVA, a supermicrosurgery approach is applied to make an intima-to-intima coaptation. The implantation technique has been used by authors with successful results [48,49], but the implanted tunica adventitia can cause a blood clot inside the vein although a vein with intact valves cannot guarantee reflux. A secure physiological anastomosis can be achieved by LVA because it follows the principal of vascular anastomosis that intravascular lumen should only be covered by endothelium. A recent animal study has revealed the patency of LVA was higher than lymphovenous implantation in 1 week after operation [50].

The effectiveness of LVA depends on the functional lymphatic vessels and suitable vein or venules with intact valves to prevent venous backflow. ICG lymphography has been used to identify intraoperative functional lymphatic vessels and venules, as well as ultrasonography (US) and vein visualizer can also be helpful when ICG lymphography cannot visualize those vessels [51–53]. In lymphatic supermicrosurgery, venous backflow rate, technical difficulty, and bypass efficacy are important points to be recognized in making decision for anastomosis. There are 4 basic types of anastomosis in LVA: 1. End-to-end; 2. Side-to-end; 3. Side-to-side; 4. End-to-side. Side-to-end or side-to-side drain more lymph fluid compared to the other 2 types because antegrade and retrograde lymph fluid flow to a single anastomosis. Among all, end-to-side anastomosis carries higher risk of venous backflow and thrombosis [54].

The outcome of LVA for UEL has shown promising results. Koshima et al. [55], analysed UEL patients who underwent LVA plus bandaging or only used compression garment. In bandaging only group, the arm circumference reduction was only 0.8 cm after 10.6 months of follow up, while in LVA plus bandaging group, the decrease was 4.1 cm in 2.2 years. He recommended LVA and post-operative bandaging for UEL cases. Another large study of UEL was conducted by Chang et al. [56]. In 89 LVA, the subjective improvement could be achieved in 96% patients and the average of volume reduction in 72% patients was 42% at 12 months. Based on ICG lymphography's M.D. Anderson lymphedema classification, stage 1 or 2 had a mean volume reduction of 61%, but in stage 3 or 4, the mean volume reduction could only be obtained until 17%. No patients experienced UEL progression during the study. A recent systematic review described 7 LVA studies and the reported excess circumference reduction was 48.9% [57]. The conclusion which can be drawn from these studies is, LVA for UEL will have its potential effects in early stage of disease. In advanced stage, lymphatic hypertension will degenerate endothelium and SMC, leading to lymphosclerotic with the loss of lymphatic function to drain lymph fluid. In this stage, VLNT should be considered as another options [58]. LVA is a promising surgical intervention, but a better study design and longer follow up are needed to confirm its efficacy.

Vascularized lymph node transplant (VLNT)

VLNT is another type of a physiologic surgical treatment. Lymph nodes with their supplying vessels are transplanted in regions where the lymph nodes dissection has been performed. The lymph nodes can also be placed in distal sites of lymphedematous limbs. Initially, it was the animal study of Shesol et al. [59] which delivered the concept of VLNT as a reliable method. Their study confirmed that after lymphadenectomy, the restoration of lymphatic function occurred in the transplanted site after VLNT, and also proved that non VLNT group could not be used as a surgical option because no lymphatic vessels identified in microscopic examination. The clinical application of VLNT was then conducted by Clodius et al. [60]. They reported the important of lymphatic axiality within the flap and recipient site, functionality of flap's lymphatic system, intimate contact of lymphatic donor and recipient site, and minimal scar tissue which could inhibit lymphaticolymphatic connection.

The first basic theory of VLNT is promoted by lymphatic restoration via lymphangiogenesis [61]. It has been recognized that vascular endothelial growth factor (VEGF)-C and -D regulate the mechanism [62]. It is also evidenced that human's lymph nodes contain VEGF-C which promotes regrowth of lymphatic vessels [63]. After the recipient and donor site vessels reconnected, lymphatic fluid drains through the lymph nodes' efferent vessels or via LVC within the nodes [64]. The second theory is based on “lymph pumps” mechanism as proposed by Cheng et al. [65,66]. The Starling's force wherein high pressure gradient between high-pressure arterial inflow and low-pressure venous outflow will drain lymph fluid from interstitial tissue through the low-resistance lymph capillaries and finally to the vein system via the high-endothelial venules (HEV), which serve as the functional anatomic site for LVC. As the interstitial pressure decreases, the “catchment effect” of VLNT will recruit more lymph fluid into the nodes [65,67,68].

Several donor sites are selected for VLNT. The anatomy location can be categorized in cervical, axilla, groin, and abdominal cavity. In cervical area, submental and supraclavicular lymph nodes flaps are the most commonly used. Submental flap is based on submental artery. The average nodes can be found is 3.0 ± 0.6. The flap has a reliable anatomy vascularization but the risk of marginal mandibular nerve damage and visible scar become its limitation. On the other hand, a well-hidden scar could be the benefit of supraclavicular flap. The vascularization comes from transverse cervical artery but variability and tedious dissection are the disadvantage of this flap. Attention must be taken not to injure thoracic duct. Vascularized thoracic flap can be based on lateral thoracic or thoracodorsal artery. An average of 5–7 lymph nodes can be found [69,70]. Although the anatomical location of lateral thoracic artery can be varied, Tashiro et al. [71] underlined he usefulness of color Doppler ultrasound to find the vascularity. Three branches are identified namely, superficial, medial and deep branch. Risk of donor site lymphedema become the drawback. Groin flap is the most common used flap in VLNT. The superficial circumflex femoral artery give its vascularization. It has a reliable anatomy and could be harvest along with deep inferior epigastric (DIEP) flap for breast reconstruction. Small and short size artery, and also the risk of lower limb lymphedema are the disadvantage of groin flap [69]. Gastroepiploic and jejunal lymph nodes flaps are another option. Eliminating the risk of donor site lymphedema is the benefit of these flaps, but entering the abdominal cavity could increase the risk of abdominal complication [69,72]. Although groin and lateral thoracic VLNT carry a risk of donor site lymphedema, reverse lymphatic mapping technique can be done during lymph node harvesting to establish a safety VLNT [73].

The recipient cites is divided into proximal and distal anatomic sites. Axilla is the proximal anatomic sites for UEL whereas groin is selected for LEL. The distal anatomic sites include elbow and wrist for UEL or knee and ankle for LEL. Proponent of proximal implantation believe the functionality of VLNT is based on lymphangiogenesis and low venous pressure at proximal site, while surgeons who prefer distal anatomic sites convincing the lymphatic pump theory as the main mechanism [68]. The results of VLNT has shown a consistent efficacy from 2 meta-analysis studies. Basta et al. [57] found 48.5% excess circumference reduction and a recent study by Carl et al. [74] showed 39.5% excess circumference reduction.

Specific issue

Several interesting topics are subjected for future development. The efficacy of LVA relies on the anastomosis of functional lymphatic vessels. Preoperative localization for these vessels is difficult in dermal backflow pattern ICG lymphography. Hayashi et al. [52] has proven the utility of US in conjunction with ICG lymphography for a successful LVA. US identified larger vessels caliber and high flow lymphatic fluid. Not to mention, finding suitable veins with less reflux can also be guided with US. Conducting further studies in US guided LVA would be an interesting issue to achieve a better outcome in LVA.

Another interesting point is the concept of lymph axiality-based (LAB) flap transfer which was proposed by Yamamoto et al. [75]. Lymph flow restoration can be achieved when a free flap is transferred with compatible lymph axiality without raw surface in lymph axiality in the donor-recipient site. LAB flap offers a more physiologic lymphatic reconstruction. The advantage of the technique is that supermicrosurgical lymphatic anastomosis or VLNT is not needed. It has potential effect of eliminating the risk of donor site lymphedema from VLNT. The efficacy of the technique in prevention or treatment of lymphedema after breast cancer treatment will become an important future studies. LAB flap can be easily combined with conventional abdominal flaps. Therefore, simultaneous breast reconstruction and lymphedema treatment is possible by the use of deep inferior epigastric perforator LAB flap.

Basic molecular knowledge has opened up new aspects in lymphedema research. Connexin 47 has been identified in lymphedema after breast cancer treatment. Identifying high risk patients from a genetic point of view would effect to the treatment

strategy. A preventive surgery could be considered and also the plan for adjuvant chemotherapy or radiation must be well discussed in high risk patients [76]. The invention of VEGF-C and -D as lymphagiogenic factor has brought out the field of molecular study to support the efficacy of lymphatic microsurgery [77].

Conclusion

The development of microsurgery has substantiated lymphedema research and treatment in recent years. Many aspects of diagnostic, surgical treatment, and follow up need to be refined and standardized. In specific to breast cancer field, the knowledge of lymphedema and lymphatic research will give a significant influence to its care. Basic science study, molecular research, and refinement of lymphatic microsurgery reconstruction will hold the future of lymphedema treatment.

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