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Management of Lymphedema

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Lymphedema is a frequent complication after the treatment of various cancers, particularly breast cancer, gynecological cancers, melanomas, and other skin and urological cancers. Lymphedema patients have chronic swelling of the affected extremity, recurrent infections, limited mobility and decreased quality of life. Once lymphedema develops, it is usually progressive. Over time, lymphedema leads to fat deposition and subsequent fibrosis of the surrounding tissues. However, there is no cure for lymphedema. Recently, the development of microsurgery has led to introduction of new surgical techniques for lymphedema, such as vascularized lymph node transfer. We report here the latest trends in the surgical treatment of lymphedema, as well as diagnosis and conventional treatments of lymphedema.

Key Words: Lymph node, Surgical anastomosis, Lymphedema

INTRODUCTION

Lymphedema is a chronic, progressive condition caused by an imbalance of lymphatic flow.[1] Over time, lymphedema leads to fat deposition and subsequent fibrosis of the surrounding tissues.[2] These chronic changes are irreversible and are painful and debilitating to a patient's daily activities.

Lymphedema is classified into primary and secondary types. Primary lymphedema results from genetic or developmental anomalies, while secondary lymphedema results from postnatal causes including infection, trauma, surgery, and radiation.[3,4] Worldwide, the leading cause of lymphedema is filiriasis, a parasitic infection caused by the roundworm Wuchereria bancrofti, which mostly affects developing countries.[5] In developed countries, however, the leading cause of lymphedema is the consequence of oncologic therapies. It can be a dreaded and not uncommon complication from the treatment of various cancers, particularly breast cancer, gynecologic cancers, melanomas, and other skin cancers and urologic cancers. Additionally, elements, such as obesity, extent of axillary surgery, radiotherapy, infection, and trauma, have been identified as factors predisposing to lymphedema.[6-8]

Recently, the prevalence and incidence of breast cancer-related lymphedema has been increasing rapidly in most countries. Breast cancer-related lymphedema impacts on average 21% of breast cancer patients,[9] although incidence rates can range from 2% to 65% depending on surgical, radiation, and systemic therapy treatment decisions as well as patient specific factors.[10] More aggressive local therapy (mastectomy vs. breast conservation), axillary surgery (axillary dissection vs. sentinel node biopsy), radiation therapy (regional nodal irradiation), and use of systemic therapies are all associated with increased risk of lymphedema.[9,10] Recent studies have found the incidence of breast cancer-related lymphedema to be 10% to 40% with regional nodal irradiation and 10% to 50% with axillary dissection.[11-14]

Lymphedema has always been considered an intractable disease. Recently, due to the development of microsurgery, new surgical techniques for lymphedema, such as vascularized lymph node (VLN) transfer have been introduced. Therefore, the authors tried to report on the latest trends in the surgical treatment of lymphedema as well as diagnosis and conventional treatments of lymphedema.

DIAGNOSIS

Clinical diagnosis

Physical examination features classically unique to lymphedema include peau d'orange changes of the skin, indicating cutaneous and subcutaneous fibrosis,[15] and a positive Stemers sign (the inability to grasp the skin of the dorsum of the second digit) (Fig. 1). Documentation and diagnosis of lymphedema has classically been made through circumferential measurements or volume/water displacement comparing the patient's affected and unaffected limb (>2 cm limb difference or a volume differential of greater than 200 mL). Water displacement offers perhaps the most accurate measurement; however, this is impractical in many situations and thus seldom used.

There are several classification scales for lymphedema. However, the most commonly accepted is based on the International Society of Lymphology (ISL),[16] which encompasses stage 0 to III based on 2 factors: the "softness" or "firmness" of the limb and the outcome after elevation.[13] Stage 0 patients have subclinical impairment of lymphatic transport while stage III features signs of near complete lymphostasis manifesting as fat deposits, acanthosis, warty overgrowth, and other trophic skin changes.[16] This staging system reflect the natural history of lymphedema with the acute, subclinical phase potentially becoming the chronic, irreversible phase of the disease.

Fig. 1. Positive Stemers sign.

LYMPHATIC IMAGING AND MAPPING

Lymphoscintigraphy

Lymphoscintigraphy is an objective and reliable non-invasive imaging modality used to diagnose extremity lymphedema, characterize its severity, and assess post-therapeutic results.[17] Currently, lymphoscintigraphy is considered the goldstandard imaging modality for the diagnosis of patients with lymphedema and for evaluation of lymphatic disorders in the swollen extremity.[18,19]

Lymphoscintigraphy is a lymphatic mapping technique which uses subcutaneous injection of radiotracer colloid into the affected upper or lower extremity, gentle local massage to enhance uptake from the interstitial fluid, and subsequent gamma camera imaging of lymphatic vasculature.[20] The study provides information regarding both lymphatic anatomy as well as lymphatic function.[21] Typical abnormalities seen in patients with lymphedema include absent or delayed radiotracer transport, cutaneous flare, dermal infiltration or backflow, and poorly visualized lymphatic collectors and lymph nodes.[22] Calculation of the transport index is useful to semiquantitatively ascertain the severity of lymphedema and provide insight into any anatomic abnormalities, such as areas of obstruction or a reduction in the number of visualized lymphatic channels.[23] Lymphoscintigraphy possesses a high sensitivity as a lymphedema evaluation tool, but lacks standardization.[17,24]

Magnetic resonance lymphangiography

Magnetic resonance lymphangiography (MRL) has been developed to provide superior high-resolution anatomic images of the lymphatic system and detailed characterization of the soft tissue changes associated with lymphedema.[25] It is possible to get detailed limb circumference measurements from which limb volume can be calculated. To help distinguish lymphatic channels from veins, intravenous injection of ferumoxytol can be performed during MRL to isolate the contrast enhancement of veins and eliminate these signals using novel techniques.[26]

MRL is a good screening method to determine whether a patient has functioning lymphatics, the characteristics of the limb, and whether any nodal basins can be visualized. This can help guide the surgeon to choose the best possible procedure for the patient, as patients with significant fibrosis and minimal edema seen on MRL would likely not benefit from the physiologic type of procedures.

Near-infrared fluorescence imaging, indocyanine green

Indocyanine green (ICG) is a tracer that is injected in the dermis and visualized with the near-infrared (NIR) technology. When injected intravenously, ICG does not contain any active metabolites, which facilitates rapid processing and excretion into bile without secondary effects.[27] High-performance optics and NIR detectors are able to visualize relatively high resolution images up to several centimeters into soft tissues.[28] This technique evaluates the lymphatic channels in real time.

The tracer has a short half-life which allows for repetitive application, making it a convenient, minimally invasive, and suitable method for preoperative, intraoperative, and postoperative lymphatic channel evaluation.[29,30]

Different patterns of diffusion of ICG can be used to grade the severity of lymphedema. The linear pattern is normal, whereas splash, stardust, and diffuse patterns indicate increasing severity of lymphedema and increased levels of fibrosis in the lymphatic channels (Fig. 2).[31]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lymphedema is broad and includes systemic causes of edema, such as congestive heart failure, renal failure, malignancy, and protein losing conditions, and local etiologies, including lipedema, deep vein thrombosis, chronic venous insufficiency, myxedema, cyclical, and idiopathic edema.

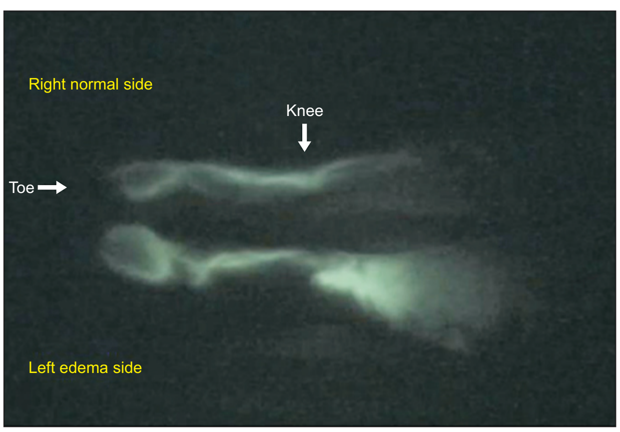

Fig. 2. Indocyanine green fluorescence lymphogram shows dermal back flow in the left leg.

CONSERVATIVE TREATMENT

Conservative treatments have traditionally been the mainstay and continue to be the initial form of treatment for all stages of lymphedema. The nonsurgical treatment includes manual lymphatic drainage (MLD), complex decongestive therapy (CDT), and the use of compressive garments.

CDT is the hallmark of conservative lymphedema management. CDT is a noninvasive multimodality treatment that includes MLD, skin care, compression bandaging, and exercises. In breast cancer-related lymphedema, the exercise component of CDT is typically conducted by a physical therapist and includes active and passive mobilization of all arm, wrist, and hand joints, ball-squeezing maneuvers, and stretching of the pectoral and trapezius muscles.[32] Another consideration of CDT is that the MLD component usually requires a skilled massage therapist.[33] CDT is time consuming, typically being performed in 2 phases with phase I involving weeks of intensive care with daily treatment sessions and phase II involving ongoing maintenance treatments less frequently.[34] CDT often requires five sessions per week for 4 to 6 weeks and the concomitant use of continuous bandaging. While these treatments can be effective at slowing the progression of symptoms, they do not address the underlying pathology and for many patients are insufficient.[35]

Other modalities used have included topical laser therapy and pneumatic compression pumps.[36,37]

SURGICAL TREATMENT

Procedures can be divided into two groups: reductive/excisional and physiologic.[38]

Reductive surgery

1) Excision

Charles[39] first described reductive procedures in 1901 for the treatment of end-stage lymphedema of the scrotum. His reductive technique involved removal of lymphedematous tissue and reconstruction with skin grafting. He later expanded his indications and popularized the technique for use in severe lower extremity lymphedemad.[40] There have been many modifications to the Charles procedure. However, these reductive procedures successfully remove diseased tissue, they are morbid, and can be disfiguring due to their large wounds and need for skin grafting.[41-43]

2) Liposuction

Suction-assisted lipectomy has been shown to be safe and effective in volumetric reduction of lymphedematous extremities. Most complications are minor and include skin parasthesias and wound healing problems at the cannulae entry sites.[38,44] Importantly, lymphatic mapping studies have demonstrated no additional damage to already impaired lymphatics after liposuction.[45] Liposuction has been shown to sharply decrease edema as well as infection rates in the lymphedematous extremity with good long-term follow-up, and it remains a major tool in the treatment of lymphedema.[45,46]

Physiologic surgery

1) Lymphovenous anastomosis

Lymphovenous anastomoses (LVAs) are indicated when the patient still has functionality of the lymphatic system, which may be assessed and documented using ICG lymphography as defined as linear channels propelling dye from the distal extremity toward the trunk. Therefore, it is generally agreed upon that LVA is easier and more effective the earlier it is performed.[47]

LVA utilize either subdermal lymphatics or the deeper epifascial system. The use of subdermal lymphatics has been championed by Koshima using supermicrosurgical techniques (0.3~0.8 mm) to create a physiologic shunt.[48-50] This procedure takes advantage of the highly complaint subdermal lymphatic system, which is responsible for a majority of regurgitant lymphatic fluid seen in dermal backflow. In addition, subdermal and subcutaneous venules are used as recipient veins and have little/no blackflow, which will create a favorable gradient following LVA. Reported outcomes using this technique have been favorable for populations with earlier staged disease.[51,52]

However, lymphatic vessels are extremely thin walled and collapse easily. Long-term maintenance of anastomotic patency following LVA cannot be ensured, but immediate patency can be demonstrated with patent blue dye or ICG lymphography.

Even with significant variance in surgical techniques, LVA has established itself as an essential tool in the management of lymphedema. In long-term follow-up of 90 patients that underwent LVA, O'Brien et al.[53] found objective improvements in 42% of patients, subjective improvements in 73% of patients and an average volume reduction in all patients of 44%. Chang et al.[47] also recently published a prospective analysis of LVA in 100 consecutive patients 12 months after LVA, finding a mean volume reduction of 61% in early-stage upper extremity lymphedema and 17% in advanced-stage lymphedema. Other studies have corroborated these findings while noting decreased volume, decreased rates of infection and relief of the use of compressive garments after LVA.[8,54,55] Complications of LVA are unusual and minimal, including infection, lymphatic fistula and wound healing problems.

2) Vascularized lymph node transfer

This method of reconstruction uses common microsurgical techniques to transfer lymph nodes to either the axilla/groin or distally in the arm/forearm/ankle. There is no accepted mechanism by which VLN transfer improves lymphedema; however, there are two leading theories. The first is that the VLN transfer functions as a "sponge" or "pump," taking up lymph into the nodes and directing it into the venous circulation through naturally occurring lymphovenous connections in the transplanted tissues.[56,57] To confirm their hypothesis, Cheng et al.[56] injected ICG directly into the edge of a VLN transfer or a cutaneous flap in both animals and humans. Fluorescence was then observed in the donor vein and then recipient vein of the VLN transfer group, indicating lymph uptake and drainage by the VLN transfer group although no fluorescence was observed in the veins of the cutaneous flap group. The other proposed mechanism for VLN transfer is via lymphangiogenesis, or by the stimulation of efferent and afferent lymphatic connections between the VLN transfer and the recipient bed. In this theory, the VLN transfer contains lymphangiogenic mediators that act locally to stimulate ingrowth and inosculation of lymphatic vessels to the VLN transfer lymphatic network.[58-60]

The harvest of VLNs has been described using groin, thoracic, submental, and supraclavicular nodes, with the groin being the most popular. More recently, other options such as mesenteric lymph node transfer and the use of omentum have been reported.[61,62] The groin flap is based off the superficial circumflex iliac vessel or the medial artery of the common femoral artery. It offers several advantages including an inconspicuous scar, reliable anatomy, the presence of multiple lymph nodes, and the ability to harvest this flap with an abdominally based flap for total breast reconstruction.[63-66] The disadvantages of the flap include the small size of the donor artery, short vascular pedicle, and the potential for iatrogenic lymphedema of the lower extremity following harvest.[67] The groin VLN flap has been critically examined as recent reports of donor site morbidity have been published related to groin VLN flap harvest.[67,68] It is advisable to harvest the laterally based nodes that drain the suprailiac region supplied by the superficial circumflex iliac artery. This is important because the lymph nodes that drain the lower limb are located medially and centrally.[69,70]

The submental flap is another flap that is gaining popularity for its use in VLN transfer. Level 1a and 1b lymph nodes are harvested based on the submental artery and vein. This perfusing artery emanates from the facial artery approximately 1 cm below the angle of the mandible and travels anteriorly toward the mandibular symphysis. The advantages of this flap include the number of lymph nodes, reliable anatomy, size of submental and facial artery, ease of harvest, limited potential for iatrogenic lymphedema, and flap thickness. In addition, the flap size is small, allowing for a smaller recipient site.[64,71] The disadvantages include the potential for damage to the marginal mandibular nerve during dissection, platysma palsy and the resulting scar on the upper neck.

The supraclavicular VLN flap has also been described as another option for VLNs. The supraclavicular VLN transfer is based off the transverse cervical vessels. It is a thin flap with an inconspicuous donor site that is attractive to many patients. Harvest of level V lymph nodes in the posterior triangle of the neck is possible based off of the supraclavicular vessels. The right neck is the preferred site for harvest given the left-side location of the main thoracic duct.

Finally, the thoracic VLN transfer is based on long thoracic or thoracodorsal artery branches that carry level I axillary lymph nodes.[6] This flap may be easily accessed during surgeries that aim to remove the significant scarring in the axilla resulting from previous axillary lymph node dissection. The donor vessels are of sufficient size and length for anastomosis, and the number of lymph nodes that can be harvested is adequate. The disadvantages include the inherent risk of causing iatrogenic lymphedema to the upper extremity. Other disadvantages include an unreliable vascular pedicle from the thoracodorsal or lateral thoracic artery, the need to sacrifice the thoracodorsal nerve and the likelihood of requiring two separate anastomoses.

Much like donor sites, the recipient sites also have variability. In treating upper extremity lymphedema, recipient sites have included the wrist, elbow, and axillary regions. As most upper extremity lymphedema results from previous surgery with or without radiation to the axilla, it is important to perform wide excision of scar that may be enveloping nerves, muscles, and recipient vessels (e.g., thoracodorsal) both to ensure a healthy bed for lymphangiogensis and to remove scar that would prevent bridging of lymphatics in the recipient bed.[72] For the lower extremity, the ankle and groin are the most common recipient sites. Similar to the axilla, the groin may often require extensive lysis or excision of scar from previous surgery and radiotherapy.[6] The superficial circumflex iliac vessels are identified superior to the inguinal ligament and used for anastomosis. The use of the ankle as a recipient site in the lower extremity follows along the logic that the gravitational forces keeping the lymphatic fluid from rising up to the groin are difficult to overcome.[73,74] Instead, placement of the VLNs at the level of the ankle would take advantage of these forces to facilitate drainage into the flap at the level of the ankle. The anterior tibialis or dorsalis pedis is used for recipient vessels, with careful attention to prevent excessive tension during flap inset, sometimes requiring skin grafting.

CONCLUSIONS

Lymphedema is a life-long disease with no cure. For those patients with ISL stage III, conservative treatments are not effective and reductive surgery is the only option. However, recently, due to the development of microsurgery, new surgical techniques for lymphedema, such as VLN transfer have been introduced. Therefore, in my opinion, before the onset of end-stage disease (ISL III), the physiologic surgeries such as LVA and VLN transfer should be performed in the patients with early staged disease that is likely to produce good long-term results.

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