

Breast Cancer Related Lymphedema

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Lymphedema is a relevant clinical problem associated with breast cancer patients. Lymphedema can occur in any area of the body, including the head and neck, trunk or upper and lower limbs. Cancer-related lymphedema can be caused not only by the disease itself but by necessary therapeutic measures such as radiation, chemotherapy, or lymphatic tissue destruction after surgery. Imbalances of capillary pressure, interstitial pressure, interstitial fluid colloid osmotic pressure, and plasma colloid osmotic pressure can lead to lymphedema. A series of complex processes contribute to the development of radiation induced lymphedema. Currently there are few tools available to diagnose early stage lymphedema, or to monitor changes in response to therapeutic intervention, although recent research has begun to address this problem. At present, commonly used therapeutic methods for lymphedema involve conservative treatment measures. More prospective studies about breast cancer survivors suffering from postoperative lymphedema are needed to help clinicians avoid unnecessary treatments and provide optimal care for patients with breast cancer.

Key Words: Lymphedema • Breast cancer

INTRODUCTION

Lymphedema is a relevant clinical problem associated with breast cancer patients. Lymphedema is a morbidity factor present among breast cancer patients that causes limb swelling, lowers the function and mobility of the affected limb, and causes paresthesia. The prevalence rate of lymphedema in the general population varies quite widely [1-3]. Lymphedema occurs when the lymphatic system is no longer working efficiently, causing a build-up of fluid in the skin and subcutaneous fat in the affected region [4].

Lymphedema can occur in any area of the body, including the head and neck, trunk or upper and lower limbs. For example, lymphedema after gynecologic cancer

treatment occurs in approximately 6% to 37% of patients [5]. The rate may be higher in breast cancer survivors, as one study found that 6 years following treatment, 48.2% of 287 breast cancer survivors experienced arm swelling at least once, and 34% showed clinical evidence of chronic lymphedema [6].

Cancer-related lymphedema can be caused not only by the disease itself but by necessary therapeutic measures such as radiation, chemotherapy, or lymphatic tissue destruction after surgery. As an example, up to 30% of breast cancer survivors (BCS) have been reported to suffer from breast cancer-related lymphedema (BCRL) after surgery [7].

BCRL normally occurs unilaterally on the side of the patient's treated area. BCRL occurs more frequently in women who have undergone axillary lymph node dissection, sentinel lymph node biopsy, and/or radiation therapy for the treatment of breast cancer.

Lymphedema can occur soon after surgery or up to decades postoperatively in survivors. After its emergence, it is a life-long condition that requires the on-going management of symptoms with daily treatment regimens to prevent progression of serious symptoms that include swelling, loss of sensation, pain, reduced range of motion, and infection.

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Around a quarter of treated breast cancer patients go on to develop lymphedema. However, at present there is no method to determine which patients will be affected. Breast cancer patients continue to develop BCRL even though more conservative cancer treatments have been used recently. BCRL can appear years after breast cancer treatment, possibly as a result of the disease being a degenerative process, which begins proximally in the affected site and spreads distally over time [4,8].

There is no standardized patient education for post-operative lymphedema or a universal standardized evidence-based treatment protocol to manage the symptoms of postoperative lymphedema [9].

MAIN

A journal review was performed searching PubMed, MEDLINE, and 75 articles were retrieved. The keywords are lymphedema, etiology of lymphedema, pathophysiology of lymphedema, etc. only English studies were included.

1. Anatomy and physiology of lymphatics

The functioning lymphatic vascular system is composed of interstitial space, body organs (thymus, spleen, and bone marrow), and lymphatics that contain fluid, immune cells, and tissue. The lymphatic system plays a major role in fluid exchange at the blood capillary-Interstitial lymphatic interface. Four forces or pressures interact to drive capillary filtration: capillary pressure, negative interstitial pressure, interstitial fluid colloid osmotic pressure, and plasma colloid osmotic pressure. In healthy persons, the arterial sides of capillaries release fluid into the interstitial spaces because these pressures create a net pressure favoring filtration [10]. Most of this fluid returns to the blood vasculature through the venous end of the capillary because of the net venous reabsorption pressures that favor venous reuptake. The lymphatic system is then responsible for removing the remaining fluid and by-products from the interstitial space. Fluid and by-products are able to enter the lymphatic system because of the unique architecture of the initial lymphatic vessels. Composed of endothelial cells, these vessels have gaps between adjacent cells and also attach to surrounding connective tissue by lymphatic anchoring filaments [3,10]. Fluid moves into the lymphatics when conditions in the tissues result in the interstitial pressure being higher than the pressure in the

initial lymphatics and the unidirectional valves in the gaps sites are forced open [10]. Upon entry into the initial lymphatics, the fluid becomes lymph. Fluid and proteins are moved through the lymphatic collector vessels and nodes by intrinsic and extrinsic mechanisms: (a) rhythmic contractions of lymphangions in segments between each valve; and, (b) lymphatic vessel compression related to the contraction of surrounding skeletal muscle tissue, respiratory effort, and arterial pulsation. The small vessels in the interstitium empty lymph into deeper vessels that connect with larger lymphatic trunks that drain into left thoracic or right lymphatic ducts located in the head and neck region of the body, and eventually into the left and right subclavian veins [10].

2. Risk factors

Studies of breast cancer survivors suggest that symptomatic seromas are associated with lymphedema [11,12]. One study of 130 breast cancer survivors found that those who experienced seromas post-treatment were 7.78 times more likely to develop arm swelling and 10.64 times more likely to develop truncal (chest and breast) swelling.[11] These findings are supported by similar results in a larger study (N = 1,054) that also identified postoperative seroma as a risk factor for the development of lymphedema [12]. Postoperative seroma can be risk factor associated with lymphedema.

It was reported that there is a strong association between lymphedema and recurrent infections in a study of 136 breast cancer survivors who had undergone treatment for breast cancer [13]. More recently, it has also been reported that infection is an independent risk factor for the development of lymphedema in breast cancer survivors [12].

Body mass index (BMI) may be associated with lymphedema that develops after breast cancer surgery [14]. One study found that breast cancer survivors who had a pretreatment BMI ≥ 30 were approximately 3.6 times more prone to developing lymphedema 6 months or more after treatment than those whose BMI was <30 at the time of treatment [15].

3. Cause of lymphedema

Imbalances of capillary pressure, interstitial pressure, interstitial fluid colloid osmotic pressure, and plasma colloid osmotic pressure can lead to lymphedema. Additionally, alteration of either extrinsic or intrinsic propul-

sion mechanisms of lymphatic structures can impede the passage of lymph flow, which can result in lymphedema. Unfortunately, cancer treatments can negatively impact any or all of these components that are critical to maintaining lymphatic function [10]. It is postulated that this flow increase is related to stenosis in the arterial and venous axillary and brachial vessels on the limb ipsilateral to the surgery [10,16].

Lymphedema of an upper extremity develops in relation to breast cancer surgery, particularly, axillary lymph nodes dissection. Surgical removal of the normal lymphatic system includes nodes, vessels, and peripheral tissue. Surgical procedures can alter normal anatomic structures and lymphatic routes, which can disrupt the lymphatic transport system, lymph transport [16,17].

In recent studies, it has been reported that there is a relationship between taxanes and lymphedema. In 2007, Vignes et al. [18] reported that, out of 1,693 patients seen in 1 year, 24% had received docetaxel. Three years later, in a patient group with taxanes, lymphedema was prominent (20%) than without taxanes (11%) [19]. Although more studies are needed, there is the possibility of a relationship between one group of chemotherapeutic agents and lymphedema [10].

A series of complex processes contribute to the development of radiation induced lymphedema [10]. Initially, radiation causes DNA and non-DNA damage with the generation of reactive oxygen species and release of inflammatory mediators [20,21]. Pro-inflammatory cytokines stimulate connective tissue disintegration and decreased oxygen to epithelial cells, causing cell damage and death. Non-DNA mechanisms, radiation can also cause fibrosis of the lymph nodes [22]. Signal amplification and gene up-regulation increase initial damage [20,22]. Finally, bacterial colonization results in stimulation of mononuclear cells to produce and release pro-inflammatory cytokines that likely increase tissue injury by promoting expression of proapoptotic genes [20]. acute inflammation manifests as soft tissue edema that may resolve [8].

To sum up, radiation causes tissue damage, node damage, and fibrosis, resulting in loss of function and may potentially impair lymph transport in patients who have been treated with radiation. This can lead to lymphedema in any part of the body exposed to radiation [10].

However, not all patients who underwent similar surgical procedures and radiation develop lymphedema. This suggests that there may be individual factors that make a difference. Initial published studies have found genetic mutations in hepato growth factor receptors/high

affinity hepato growth factor receptors (HGF/MET) [23] and in Connexin [24] (Cx47) in breast cancer survivors with secondary lymphedema. This suggests that genetic mutations could influence the molecular and biological processes involved in maintaining lymphatic function.

Genetic studies are now underway to examine secondary lymphedema in other tumor types. This ongoing work may soon enable clinicians to identify patients with genetic profiles that place them at risk for secondary lymphedema after cancer treatment and modify treatment or lead to the implementation of risk-reduction practices based on such information [10].

4. Diagnosis

Currently there are few tools available to diagnose early stage lymphedema, or to monitor changes in response to therapeutic intervention, although recent research has begun to address this problem [25]. The gold standard is the measurement of volume, which can be performed either by measuring the limb-circumference with a tape measure and calculating the volume using water displacement volumetry or by using optical methods [2]. In addition to the confusion surrounding changes in each layer of tissue, the volume measurement technique suffers from the disadvantage that it can only detect lymphedema when the variation between limbs is bigger than the normal variation of 4% between a healthy person's dominant and non-dominant limbs [2]. Therefore the technique is not ideal for identifying changes in limb volume in early stage lymphedema. In addition, the site of swelling can vary from patient to patient, and not all patients suffer from swelling over the whole limb. Changes in volume cannot easily be measured on the hands and the quadrant of the trunk. The volume technique is therefore only useful on the limbs themselves. For example, recent changes in breast cancer surgery mean that patients are now undergoing more conservative treatments; lumpectomies are commonly carried out rather than mastectomies. This has led to an increase in the incidence of lymphedema in the breast itself, for which standard volume measurements cannot be used. In addition, lymphedema occurring in other body sites such as the head and neck, trunk, lower limb cannot be diagnosed with such techniques, and would therefore benefit from the development of novel, localized diagnostic techniques [26].

Limb volume was evaluated by different methods. Such methods were used in different studies: water displacement volumetry, limb circumference measurements, bio-impedance spectroscopy, dual X-ray absorptiometry (DXA),

and perometry [6,27-31].

5. Treatment

At present, commonly used therapeutic methods for lymphedema involve conservative treatment measures. These are designed to serve as transport assist mechanisms to help move fluid from affected areas to unaffected areas of the lymphatic system. Examples of external transport assist mechanisms include: manual lymphatic drainage, compression garments, bandaging, intermittent pneumatic compression devices, and exercise [10]. to prevent or control postoperative lymphedema, and conservative treatments are also required, such as complex decongestive physiotherapy combining manual lymph drainage, skin care, compression, exercise, and pharmacotherapy temporarily [32]. However, these treatments cannot lead to a complete cure. Although new surgical treatments-including lymphatico-venous anastomosis, micro surgical techniques for lymphatic grafting, and omental J-flap placement — have been recently reported, these methods involve lengthy operations; furthermore, their results are not always satisfactory [32-34].

CONCLUSION

Breast cancer is a common malignancy in women, and of those who contract breast cancer, more than 20% of those who survive breast cancer will develop secondary lymphedema [1,35] which is associated with a number of major impairments that affect daily activities and which lead to a substantial reduction in quality of life [3,7].

Although a number of studies and researches are being conducted in relation to the treatment of postoperative lymphedema, clear conclusions have not been established yet. More prospective studies about breast cancer survivors suffering from postoperative lymphedema are needed to help clinicians avoid unnecessary treatments and provide optimal care for patients with breast cancer.

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