

## REVIEW ARTICLE

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# Diagnosis, treatment and quality of life in patients with cancer-related lymphedema

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## Summary

Cancer-related lymphedema is the result of surgical operation or radiation therapy of the corresponding lymph nodes and is due to the obstruction of the lymphatic drainage in the affected area. In lymphedema the lymphatic stasis causes an inflammatory reaction that leads to the proliferation of adipose tissue and fibrosis, resulting in mild to severe permanent swelling of the affected part of the body. It is more often found in the upper extremities of women with breast cancer. It may, however, appear at one or more extremities and may include the corresponding quadrant of the trunk. It may also affect head and neck, breast, genitals and lower extremities, depending on the surgery the patient has undergone. It is often associated with obesity (BMI>40). Early diagnosis and treatment of lymphedema is related with better

therapeutic outcome. Women with breast cancer confront more problems with lymphedema than with mastectomy. Its effect on patients' quality of life is relevant to changes in body image, self-esteem, feelings of weakness, fear and anxiety about disease progression, financial costs, and reduced limb function. More recent studies support the effectiveness of contemporary surgical techniques in lymphedema's treatment. In conservative management, CDT remains the treatment of choice and in combination with exercise, weight control programs and self-care training seems to significantly improve patients' quality of life.

**Key words:** cancer patients, diagnosis, lymphedema, quality of life, treatment

## Introduction

Lymphedema of the corresponding limb is mainly the result of surgical operation or/and radiation therapy of the corresponding lymph nodes and is due to the obstruction of the lymphatic drainage in the affected area. In lymphedema the lymphatic stasis causes an inflammatory reaction that leads to the proliferation of adipose tissue and fibrosis, resulting in mild to severe permanent swelling of the affected part of the body [1-3]. It is more common, as side effect, in treatment of cancer patients, especially in the upper extremities of women with breast cancer associ-

ated with surgical removal of the axillary lymph nodes and fibrosis after radiation therapy [4]. It is most commonly reported in the upper extremities of women with breast cancer associated with surgical removal of the axillary lymph nodes and fibrosis after radiation therapy. However, it can occur at one or more extremities and may involve the corresponding quadrant of the trunk. It may also affect head and neck, breasts, genitals and lower extremities, depending on the surgery the patient has undergone. It is often associated with obesity (BMI> 40) [5].

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Its prevalence varies depending on the diagnostic criteria used, the reference population and the duration of follow-up. It is more common in those who have had their axillary lymph nodes surgically removed and may appear a few days or 6-8 weeks after surgery or radiotherapy. Although the risk of developing lymphedema in women remains up to 20 years later. In most cases, lymphedema will appear within the first three years after surgery. Lower extremity lymphedema occurs in up to 80% of people who have had inguinal lymph node surgical removal or those who have pelvic or inguinal lymph node compression [3]. Approximately 20% of women develop lymphedema after treatment for breast cancer [6]. The increase of limb's perimeter  $\geq 10\%$  should be a criterion for referral to a health professional [7].

The investigation of cancer-related lymphedema is essential because lymphedema has a strong impact on patients' physical, psychological and social health, affecting directly on their quality of life [8]. Women with breast cancer confront more problems with lymphedema than with mastectomy. Studies focus on identifying all the dimensions that are affected, especially the physical, emotional, social and cognitive dimension. Continuous monitoring and assessment of the disease include not only the evaluation of cancer complications but also treatment side effects and patient's quality of life. The evaluation significantly determines the needful interventions [9], and each time sets the limits of patients' education in self-care, aiming to reduce lymphedema's occurrence and improve the quality of life [10-12]. Early action seems to enhance the effectiveness of interventions [13]. At the same time, continuing care with potentiating self-care can have psychological and behavioral benefits and contribute to the optimization of self-management [14].

## Diagnosis and staging

Early detection and intervention are crucial for effective for the management of this situation [15,16]. Assessing the risk of lymphedema in cancer patients at the start of the treatment such as radiotherapy and follow-up, are useful interventions in the promptly assessment of possible changes over time [16].

Lymphedema is possible to occur in many areas of the body such as the upper extremities, lower extremities, genitals, breast, head, neck and in patients undergoing therapy for a variety cancer diagnosis [17]. Due to the swelling, patients may develop chronic pain, anxiety or depression, symptoms that also need to be evaluated, as well

as difficulties in the range of motion, elimination in daily activities and walking, arthralgias and difficulty in using ordinary clothing [18].

Various methods for measuring lymphedema have been used in clinical practice and research. Quantitative methods include fluid displacement (gold standard, but impractical for clinical use), volume calculation based on the perimeter of the circumference by tape measurements in cm and use of a mathematical formula, measurement of circumference by infrared laser (optoelectronic perometry) and Bioelectrical Impedance Analysis (BIA). Volume calculation based on perimeter circumference by tape measurements in cm and the use of a mathematical formula is the most widely used method in clinical practice. Nevertheless, a reassessment of all diagnostic methods seems to be needed [19] as accurate measurement of lymphedema in many areas and its treatment is difficult [17].

The most commonly used lymphedema assessment tools are the Lymphedema and Breast Cancer Questionnaire (LBCQ) (available from Armer@Missouri.edu), which is completed by phone and is available via email, the Limb Lymphoedema Quality of Life (LYMQOL), which is filled in by the patient (available from vaughan.keeley@derbyhospitals.nhs.uk) and the Gynecologic Cancer Lymphedema Questionnaire (GCLQ) for the evaluation of lower extremity lymphedema associated with gynecological cancers [20].

The onset of lymphedema is not always obvious. Studies in women with breast cancer have shown that some of them develop symptoms of lymphedema without objective changes in the periphery of the arm, suggesting that clinical trials may underestimate the incidence of lymphedema [21].

The addressing of the problem requires a careful diagnostic approach, based on a detailed medical record, including family record. A subsequent thorough clinical examination takes place that will exclude other possible causes and detect significant clinical signs and characteristic changes in the skin and the underlying tissues of the suspect area such as hyperkeratosis, dermatitis, redness of the skin, ulcers, blisters and nail irregularities [22].

As there is no effective method of measuring swelling of head and neck, chest, trunk or genitals, it is recommended the use of digital photography to record and evaluate lymphedema of face and genitals. Evidence-based literature also recognizes the use of more subjective methods for measuring lymphedema. Patients with limb lymphedema may experience subjective changes in limb volume, while measurable changes are absent, demonstrating the importance of recognizing self-reported symptoms [22].

**Table 1.** Staging criteria of lymphedema (International Society of Lymphology, 2020)

Stage	Criteria
0	A latent or subclinical condition, where the swelling is not apparent despite insufficient lymph transport, limited alterations in the composition of lymph fluid and tissues, and limited extent of the underlying symptoms. It may be months or years before the swelling appears in the later stages (I-III).
I	Early accumulation of fluid with a relatively high protein content (eg compared to venous edema) that subsides with limb elevation. Pitting may occur. There may be an increase in regenerative cells in the area.
II	Wider changes in anatomical structures are observed. Development of subcutaneous fat and fibrosis that cause swelling of the limb that rarely subsides with limb lifting and motor dysfunctions occur. The skin ruptures are obvious.
III	Lymphostatic elephantiasis with changes in the skin, trophic skin changes such as acanthosis with further deposition of fat and fibrosis.

The International Society of Lymphology (ISL) describes four broad stages that can be used to classify lymphedema (Table 1) [22].

### Lymphedema's treatment

Lymphedema's treatment remains a major challenge for both patients and health professionals. A standard protocol for managing lymphedema includes Complete Decongestive Therapy (CDT) which consists of Manual Lymph Drainage (MLD), Daily Compression Bandaging (CB), and skin care. This procedure involves two stages: an intensive reduction phase and an additional maintenance phase to stabilize the lymphedema tumor. It should be noted that the results depend on a large extent on patient's compliance [3,23,24].

Another method of treatment is the Intermittent Pneumatic Compression (IPC), which is widely used in the treatment of lymphedema as a supplement to CDT. It is useful in cases where passive patients are treated, ie elderly, bedridden with also severe disabilities. The IPC exerts pressure that mimics the action of the muscle pump, which is an important lymph transport mechanism. It also reduces lymphedema, preventing capillary infiltration and lymph formation. However, today the use of IPC with pump devices is controversial, as the positive expectations from their use have not been verified in practice [3,23,25].

Apart from the conservative treatment of lymphedema, more recent studies support the effectiveness of contemporary surgical techniques in lymphedema's therapy. Such surgical methods are Vascularized Lymph Node Transfer (VLNT), Lymphaticovenous anastomosis (LVA), lymphatic-lymphatic bypass (LLB) and Circumferential Suction-Assisted Lipectomy (CSAL) [3,22,26].

Regarding pharmacological treatment, diuretics are not recommended, but have limited use in some selected patients at the beginning of CDT as a complementary therapy. Antimicrobial agents are indicated in some cases for the treatment of bacterial and fungal skin infections associated with acute lymph stasis, subcutaneous tissue and nail infections, such as erysipelas, cellulitis, lymphangitis and onychomycosis that deteriorate lymphedema. Fungal infections can often be treated with terbinafine or fluconazole, carbamazepine, albendazole and ivermectin. Benzopyrones (especially coumarin) stimulate macrophages, increase proteolysis and help catabolize proteins and reduce fibrosis in the area of lymphedema. Care and hygiene of the limbs is very important to prevent opportunistic infections and the wash of the skin with a mild antiseptic followed by the use of antifungal / antimicrobial cream may be helpful [3,22].

Among the complementary and alternative therapies, Low-Level Laser Therapy (LLLT) is the only method that has demonstrated some effectiveness in the treatment of lymphedema [27]. Another type of treatment is shock wave therapy, which enhances cellular metabolism and appears to have anti-inflammatory action, vasodilators and neo-angiogenic drugs with controversial results [28].

There is no specific diet for simple lymphedema and there is no benefit to a limited intake of protein or fluids. It is necessary to include vitamins and fiber in the basis of a healthy diet, as well as reducing calories and lipid intake to prevent from obesity [22,29], limiting or completely avoiding alcohol, while food deprivation has been recommended for 13 hours in daily basis [30]. The evidence supporting acupuncture, yoga, hyperbaric oxygen therapy and the use of herbs in the

treatment of lymphedema is insufficient, though some of them may be able to improve physical and emotional function, positively affecting the quality of life. Psychosocial support is one of the most crucial components in the treatment of lymphedema [3,22,31].

### Quality of life and lymphedema

Lymphedema have a significant effect on patients' quality of life. A mixed qualitative and quantitative study [32] of 213 patients compared the impact of lower extremity lymphedema symptoms to patients' quality of life. The Lymphedema Symptom Intensity and Distress Survey-Leg (LSIDS-L) questionnaire and an additional open quality question were used for the study. The majority of the participants reported psychosocial symptoms, such as depression (65.9%), anxiety about appearance (81.9%), negative perception of body image (67.8%), fatigue (75.7%), weakness performing leisure activities (65.2%) and reduced physical activity (69.5%). The study also featured that there were patients who had no financial resources for compression garments and treatment, while they also reported an apparent lack of availability of specialized lymphedema health professionals. Patients with lower extremity lymphedema, regardless of the cause, referred significant physical effects, functional disorders [32] and severe burden, especially in primary lymphedema [33].

According to another study, physical effects (beyond swelling and heaviness) often included recurrent infections, such as cellulitis, clinical signs of lower extremity infections that required hospitalization, as well as ulcers, scars, blisters, and injuries. The exudation of ulcers was particularly problematic in its management because patients had to use additional materials, a process that is time consuming and requires significant financial costs. Therefore, the physical, psychological, economic and social consequences experienced by these patients significantly reduce their quality of life [32].

In the context of a large multicenter study (LIMPRINT), the quality of life of 1094 adult patients with chronic lymphedema (> 3 months) of upper and / or lower extremities was assessed. Patients with lymphedema in the upper extremities scored better in all dimensions of quality of life and less discomfort from symptoms than those with lymphedema in the lower extremities. It's worth noting that the quality of life was considerably higher when the patient was younger, non-obese and male [34].

### Various treatment approaches and quality of life

A comparative study included 55 women with cervical cancer who underwent postoperative radiation (with or without chemotherapy) and whose quality of life was investigated. Women were divided into 3 groups: the first group received External Beam Radiation Therapy (EBRT) with or without cisplatin 40 mg / m<sup>2</sup>, the second group received Three-Dimensional Conformal Radiation Therapy (3DCRT) and the third group received Intensity Modulated Radiotherapy (IMRT). Overall quality of life was not significantly affected by the type of radiotherapy, though it was improved after 12 months compared to the quality of life that patients had at the start of the treatment approaches in all groups. The dimension of emotional and social functionality was better in the IMRT group. Similarly, the IMRT group had higher scores on pain, fatigue, nausea and vomiting, insomnia, loss of appetite, and diarrhea. Symptoms of lymphedema and menopause were more improved with IMRT compared with 3DCRT [35].

Various compression techniques are an integral part of therapeutic intervention as they reduce lymphedema and improve quality of life [36], with the use of kinesio taping being advantageous over compression garments [37]. In a study comparing the quality of life of patients with lymphedema with magnet tape therapy (Kinesio Taping - KT) and elastic garment therapy ((Pressure Garments-PG) participated 66 women with breast cancer (stages II and III), with treatment aiming to maintain limb volume. Patients in the KT group were taped twice a week, while patients in the PG group were applied by a pressure garment (20-60 mm Hg) for at least 15 to 18 hours a day for 3 weeks. Both groups received an exercise program at home in the form of a series of movement exercises that included shoulder flexion and extension, abduction, limb elevation to 180 °, external rotation / horizontal abduction, elbow flexion and extension, walking and stretching. The exercises were done three times a day with 10 repetitions each time. The KT application consisted of 1 set of 5 magnet tapes for the chest, 2 sets of 4 magnet tapes for the upper arm, 2 sets of 4 magnet tapes for the forearm and 1 set of 2 tapes for the wrist. Both groups showed improvement and particularly there was a significant amelioration in the KT group in the scores of physical, emotional, cognitive and social roles, while the PG group displayed an important improvement only in the emotional, cognitive and social dimensions and not in the physical. Furthermore, in the



KT group there was a significant improvement in the score of symptoms such as pain, shortness of breath, fatigue, appetite, nausea, insomnia and financial problems, while in the PG group no patient performed an improvement in the score of pain and fatigue [38].

### **Complete decongestion therapy (CDT) and quality of life**

CDT is the method of choice for conservative treatment of lymphedema and the quality of life of patients undergoing it, has been studied extensively [22]. A study evaluated the quality of life in 60 patients with lymphedema after mastectomy, who underwent an exercise program at the same time as CDT therapy. The conventional therapy group received MLD and low-pressure elastic garment, while the CDT group received additional therapeutic exercises and diaphragmatic breathing exercises. Both groups received treatment 5 times a week for 6 weeks. Pain and quality of life were assessed in the beginning, 4th and 6th week of treatment. Quality of life was assessed using the QLQ-C30 and QLQ-BR23 questionnaires. Patients' pain improved statistically significantly at all three time points. The CDT group had a considerably greater reduction in pain score than the control group, and appeared a significantly greater improvement than the control group at all functional and symptom scales [39].

In a systematic review investigating the quality of life of patients with lymphedema, the CDT appeared to be the main intervention, while other concurrent interventions were exercise and low-level laser therapy. Two of the studies assessed health-related quality of life with a special questionnaire for breast cancer or lymphedema. The evaluation was performed mainly immediately after the last MLD treatment [40]. MLD in combination with physical exercise versus physical exercise alone has been found to further ameliorate patients' quality of life. Patients who underwent CDT with MLD versus CDT without MLD, as well as patients with MLD and exercise versus physical exercise alone and patients with MLD and low-level laser therapy versus low-level laser therapy alone, were found to have a noticeable enhance in emotions of wellness, lymphedema-related pain,

weight and limb size, skin tension, sleep disturbances and skin infections. Patients in the CDT + MLD group had a better quality of life, mainly in the physical and mental dimensions, in the role functions and in the reduction of the pain compared to the control group. Hand and lymphedema volume decreased significantly after MLD intervention [40]. The positive results from the implementation of physical exercise programs before even the surgery and postoperatively, have been seen in other studies [41]. Despite the fact that progressive regular exercise seems to be safe without worsening the lymphedema, no significant improvement is confirmed even if compression therapy is combined [42,43].

### **Conclusions**

Early diagnosis of lymphedema is associated with a better therapeutic outcome. CDT remains the treatment of choice and in combination with an exercise program considerably ameliorates the quality of life and patients' pain. The effect of lymphedema on patients' quality of life is associated with changes in body image, self-esteem, feelings of weakness, fear and anxiety about disease progression, financial costs, and reduced limb function.

The severity of the symptoms and the discomfort they cause, appear to be more pronounced in patients with cancer-related secondary lymphedema compared to primary and non-cancerous secondary lymphedema, while patients with primary lymphedema generally report better overall health and quality of life comparing to those with secondary lymphedema.

Patients with lower extremity lymphedema have more intense symptoms and a greater reduction in limb function associated with a worse quality of life. In all cases, it is suggested in the context of rehabilitation to integrate an exercise program that will be done at home, along with the treatment applied for lymphedema, as well as training programs in self-care.

### **Conflict of interests**

The authors declare no conflict of interests.

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