Cancer-related lymphedema

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Lymphedema is an inflammatory condition caused by the accumulation of lymphatic fluid due to damage to the lymphatic system. There are 2 classifications of lymphedema: primary, which is caused by malformation of lymph vessels or nodes, and secondary, which is due to trauma, chronic lymphatic system overload, or cancer and its treatments. This article focuses on cancer-related lymphedema, which can develop within weeks, months, or years following oncologic treatments.[1] Herein we present an overview of epidemiology, risk factors, history and physical examination for clinical diagnosis, as well as criterion-standard management for this condition in the primary care setting.

What are the main functions of the lymphatic system?

The lymphatic system is a network of tissues, vascular channels, and organs responsible for moving lymph back into the circulatory system.[2] Approximately 20 L of plasma flow throughout the body's arteries and blood vessels daily. An estimated 16 L to 17 L are reabsorbed into the circulatory system, with the remaining 3 L to 4 L seeping into tissues and being recovered by the lymphatic system. The lymphatic system's main functions are to maintain fluid levels in the body, absorb digestive tract fats, protect the body against invaders that could cause illness, and remove cellular waste products.[3]

Epidemiology, pathophysiology, and risk factors of cancer-related lymphedema

The absence of a universal definition and standardized diagnostic criteria renders cancer-related lymphedema prevalence difficult to determine, and it is likely underreported.[4] Cancer location and types of treatment influence cancer-related lymphedema incidence, with estimates ranging from 5% to 83% with different malignancies.[5-8] Due to its high prevalence, breast cancer is the most common cause of secondary lymphedema among patients in developed countries.[9] Moreover, cancer-related lymphedema occurs in approximately 1 in 6 patients with a history of melanoma, sarcoma, or gynecologic or genitourinary cancer.[10] Head and neck tumours are also commonly associated with lymphedema, which can contribute to debilitating dysphagia.[11] Estimates suggest that cancer-related lymphedema affects more than 300,000 individuals in Canada.[12]

Cancer-related lymphedema can develop as a result of obstruction of lymphatic channels or nodes by tumour compression, tumour cell infiltration of the lymphatic vessels (ie, lymphangitic carcinomatosis), lymph node dissection or removal, lymphatic channel destruction from radiotherapy, or chemotherapy agents such as taxanes.[13] Other noncancer-related risk factors also increase the risk of developing lymphedema, including trauma, overweight or obese status, chronic venous insufficiency, deep vein thrombosis (DVT), and cellulitis (**Box 1**).[14,15]

How is lymphedema diagnosed?

Cancer-related lymphedema is a straightforward diagnosis based on history and physical examination findings.[4,16,17] Given the considerable psychosocial and physical burdens associated with more advanced stages, early identification of cancer-related lymphedema is

Box 1. Lymphedema site risk factors

Upper limb or trunk lymphedema
- Axillary lymph node dissection
- Radiotherapy to the breast
- Radiotherapy to lymph nodes (axillary, internal mammary or subclavicular lymph nodes)
- Chemotherapy (taxanes)
- Skin changes following axillary radiotherapy (fibrosis, radiodermatitis)
- Complications from wounds or drains
- Axillary web syndrome
- Lymphocele
- Advanced cancer
- Overweight or obese status
- Cellulitis and inflammatory skin conditions
- High blood pressure
- Procedures such as pacemaker insertion and arteriovenous shunt for dialysis
- Filariasis

Lower limb lymphedema
- Lymphatic vessel compression due to tumour location (pelvic or abdominal tumours)
- Inguinal or pelvic lymph node dissection
- Pelvic radiotherapy
- Deep vein thrombosis and post-thrombotic syndrome
- Comorbid conditions (cardiac or renal disease)
- Advanced cancer
- Overweight or obese status
- Chronic venous insufficiency
- Varicose vein treatments (stripping)
- Cellulitis and inflammatory skin conditions
- Orthopedic surgery
- Prolonged limb immobilization
- Genetic predisposition
- Filariasis

Head and neck
- Surgical neck dissection
- Radiotherapy

paramount to minimize disease progression.[1,16-18] For patients undergoing cancer treatment or with a history of cancer, family physicians can aptly screen for lymphedema risk factors and inquire about potential early signs and symptoms of this condition.

Focused history elements

In addition to a general medical assessment including previous medical, surgical, and social history, assessment of cancer-related lymphedema and other conditions associated with swelling should be performed (**Box 2**), with particular attention to congestive heart failure, renal failure, liver or venous insufficiency, and DVT.[17]

Onset is usually insidious in nature. Early signs and symptoms of upper or lower limb cancer-related lymphedema include patient reports of clothes or jewellery feeling tighter on the affected limb (eg, tightness of finger rings, wristwatches, clothing sleeves, or footwear). Sensation of fullness or heaviness complaints of the affected limb and adjacent areas (chest, trunk, pelvic, genital) are also common, while intermittent limb swelling of the cancer-treated area is pathognomonic of lymphedema.[1,19] Head and neck cancer–related lymphedema can present as partial or extensive swelling of the oral cavity and-or neck areas. Swelling is often reported as worse upon awakening, with gradual improvement throughout the day with standing and activity. Head and neck lymphedema can also occur internally in the absence of external swelling. In these cases, swallowing difficulties, voice changes, and sensation of a foreign body lodged in the throat are commonly reported.[11] While pain may be reported, severe pain is not typically suggestive of cancer-related lymphedema and thus should lead family physicians to rule out other potential underlying causes, including cancer recurrence.

Targeted physical examination

Along with body weight and body mass index measurements, evaluation of the vascular system and palpation of the lymph nodes proximal to the affected limb or area should be performed. Assessment of both affected and nonaffected limbs or areas should systematically include a series of examinations.

Box 2. Swelling complaint evaluation

- Cardinal signs: location, quality, radiation, intensity, severity, alleviating or aggravating factors, and associated symptoms
- Pattern of swelling: insidious versus acute onset, following a trigger event (eg, cellulitis, trauma)
- Nature of swelling: intermittent versus omnipresent
- Identification of nononcologic and oncologic risk factors for lymphedema
- Review of prescribed and over-the-counter medications that may contribute to edema

Dermatologic examination. This is an assessment of skin integrity, including the presence of dryness, erythema, pachydermia, and hyperkeratotic appearance (verrucous and vesicular lesions). Evidence of lymphorrhea and underlying fungal infection or open wounds secondary to chronic diseases such as diabetes should also be noted.

Pitting test. Application of firm pressure to the edematous tissue is done for at least 30 seconds. Skin indentation after release indicates pitting edema, which can be mild or more pronounced in any lymphedema stages. In advanced stages, however, pitting is usually less pronounced due to pachydermia and fibrosis.

Stemmer sign. Pinching of skin at the base of the second toe or finger assesses for thickened skin fold. Difficulty in lifting the skin indicates a positive Stemmer sign, which can be present at any lymphedema stage.

Vascular examination. This test documents presence of varicose veins and signs of chronic venous insufficiency. For lower limbs, evaluation of pedal pulses is advised if peripheral arterial disease is suspected, as compression therapy is contraindicated in this disease.

Limb volume difference should also be determined by measuring the circumference of both affected and unaffected limbs at different anatomical landmarks. Head and neck landmarks are also used to perform measurements. Serial measurements, which are typically performed by a trained therapist, aid in assessing lymphedema evolution and treatment response but are not mandatory in diagnosing lymphedema.

Although imaging is not routinely used for lymphedema diagnosis, some investigations may be warranted if another condition is suspected, such as a duplex ultrasound to rule out DVT. If peripheral arterial disease is suspected, ankle brachial index test is relevant, especially if compression therapy is considered. Based on history and examination findings, lymphedema diagnosis is classified into 4 stages (**Box 3**; **Figures 1** and **2**).[20-23]

Management

Cancer-related lymphedema is an incurable disease requiring sustained patient support and adherence to a chronic disease management model.[24] The criterion standard of lymphedema management is decongestive lymphatic therapy,[25-27] which aims to educate patients about the condition; decrease affected limb volume and fibrosis; optimize functional status; address body image concerns and improve quality of life; and promote patient engagement and self-management.

Decongestive lymphatic therapy comprises 2 phases: volume reduction and maintenance.[16,28] When indicated, the reduction phase aims to decrease the size of the affected limb to the smallest size attainable. To reduce volume, multilayer short-stretch inelastic bandages are worn

for 24 to 72 hours at a time (and then reapplied), and to increase venous and lymphatic flow, optimal skin care and regular exercises are performed. Alternatively, in patients with comorbid conditions or functional limitations, Velcro devices can be used.[14] Reduction is carried out for 2 to 6 weeks depending on reduction requirements.

The maintenance phase aims to maintain limb volume size and requires patient engagement. Best outcomes for this lifelong phase are achieved through adherence to compression therapy, healthy lifestyle habits, and risk reduction strategies.

Box 3. International Society of Lymphology lymphedema staging definitions

Stage 0
- A subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before edema becomes evident

Stage I
- This represents early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation. The edema may be pitting at this stage

Stage II
- Limb elevation alone rarely reduces swelling and pitting is manifest

Late stage II
- There may or may not be pitting as tissue fibrosis is more evident

Stage III
- The tissue is hard (fibrotic) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop

Compression therapy. Medically prescribed compression garments (eg, sleeve, glove, knee- or thigh-high stocking) are preferably worn daily for as many hours as possible during the day. These garments are prescribed in classes ranging from 15 mm Hg to 50 mm Hg depending on the affected limb and severity. Nighttime garments may also be indicated, such as those for head and neck lymphedema. Compression garments are available in standard and custom-made sizes. Prescription should also include donning and doffing instruments to encourage optimal adherence.[16,28] A tool to facilitate prescribing is available in **Figure 3**, with a printable version available from **CFPlus**.* Contraindications to compression therapy should be reviewed (**Box 4**).[14,15]

Healthy lifestyle habits. Weight management and routine physical activity are essential to promote lymphatic and venous flow.

Risk reduction strategies. As lymphedema increases the risk of cellulitis, adherence to pristine skin care is essential to minimize infection risk and wound development.[9,29]

In addition to providing support and education, family physicians can prescribe compression therapy, refer patients to certified lymphedema therapists for co-management, and ensure follow-up visits occur every 6 to 12 months, as indicated. Lymphedema associations across Canada provide educational resources for patients, registries of local fitters and therapists, and information on provincial plans for compression garment reimbursement (**Box 5**).

*A printable version of **Figure 3** is available from **https://www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Figure 1. Examples of upper limb lymphedema stages

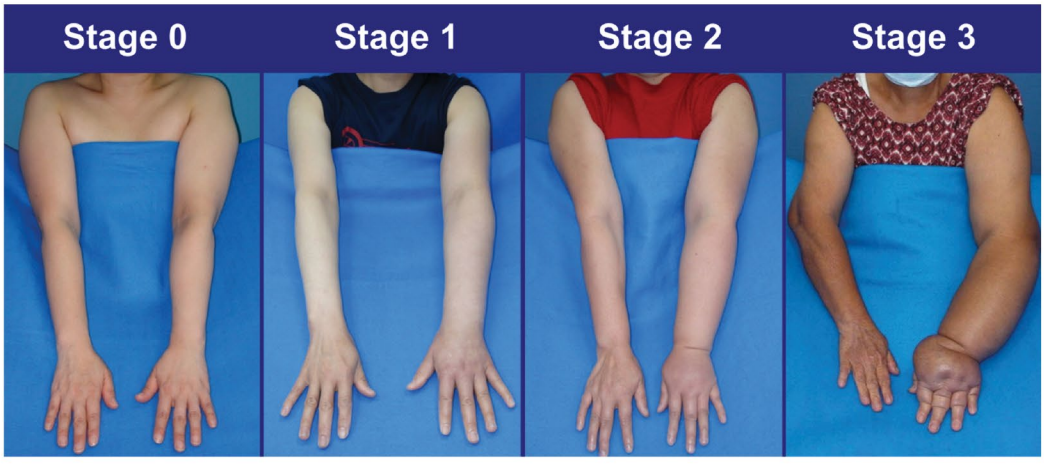

Figure 2. Examples of lower limb lymphedema stages

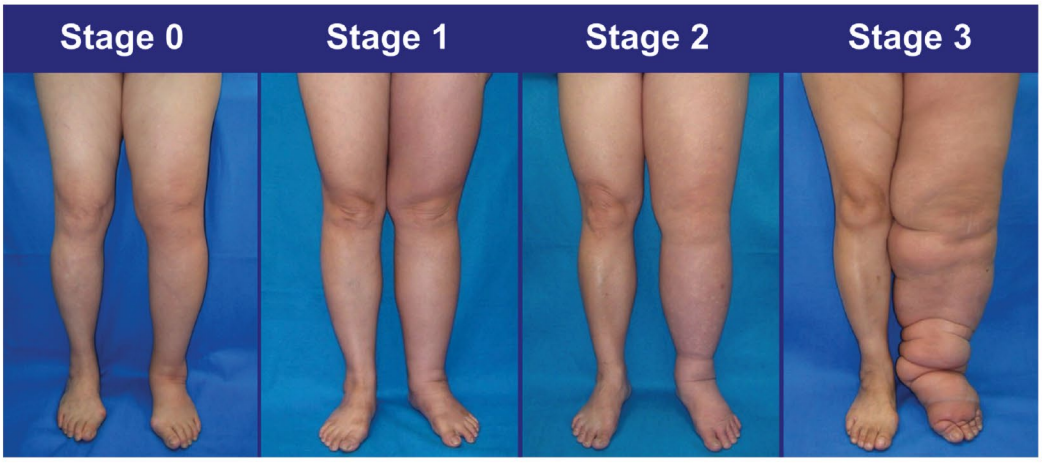

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Figure 3. Tool to facilitate compression therapy prescription

Diagnosis: right or left upper limb lymphedema
❑ Multi-layer bandage kit for reduction therapy
❑ Compression garment(s) for daytime use: ❑ Sleeve, class: ❑ 15-20 mm Hg or 15-21 mm Hg; ❑ 20-30 mm Hg or 23-32 mm Hg; ❑ 30-40 mm Hg or 34-46 mm Hg ❑ Glove, class: ❑ 15-20 mm Hg or 15-21 mm Hg; ❑ 20-30 mm Hg or 23-32 mm Hg ❑ Velcro device
❑ Compression garment for nighttime use
❑ Breast swell spot (if breast involvement)
❑ Donning and doffing instruments
Renew x 12

Diagnosis: Right, left, or bilateral lower limb lymphedema
❑ Multi-layer bandage kit for reduction therapy for right, left, or bilateral limb(s)
❑ Compression garment(s) for daytime use: ❑ Knee high, class: ❑ 15-20 mm Hg or 18-21 mm Hg; ❑ 20-30 mm Hg or 23-32 mm Hg; ❑ 30-40 mm Hg or 34-46 mm Hg ❑ Thigh high, class: ❑ 15-20 mm Hg or 18-21 mm Hg; ❑ 20-30 mm Hg or 23-32 mm Hg
❑ Compression garment for nighttime use
❑ Genital swell spot (if genital involvement)
❑ Donning and doffing instruments
Renew x 12

Diagnosis: head and neck lymphedema
❑ Head and neck compression garment
Renew x 12

Box 4. Contraindications and precautions of compression

Contraindications
- Arterial insufficiency
- Severe peripheral arterial occlusive disease
- Acute cellulitis
- Uncontrolled cardiac failure
- Acute dermatitis
- Severe diabetic neuropathy with sensory loss or microangiopathy with risk of skin necrosis
- True allergy to compression material

Precautions
- Signs of possible infection (cellulitis)
- Neuropathy
- Nonambulatory patients

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Box 5. Lymphedema associations in Canada and patient resources

Lymphedema associations
- Newfoundland and Labrador: **https://lymphnl.com**
- Nova Scotia: **https://lymphedemanovascotia.com**
- Quebec: **http://en.infolympho.ca**
- Ontario: **https://www.lymphontario.ca**
- Manitoba: **https://www.lymphmanitoba.ca**
- Saskatchewan: **https://www.sasklymph.ca**
- Alberta: **http://www.albertalymphedema.com**
- British Columbia: **https://bclymph.org**

Additional resources for patients
- Canadian Lymphedema Framework: **https://www.canadalymph.ca/patienteducationmaterials/**

Clinical pearls

Rapid, rather than insidious, onset of limb swelling associated with skin changes should trigger family physicians to rule out malignancy. Diuretics are not recommended[17]; diuretics reduce swelling via excess water removal, but proteins remain in soft tissues, thereby drawing water back, which can exacerbate lymphedema and increase fibrosis and inflammation.[30] While surgical interventions such as lymph node transfers and lymphaticovenous anastomosis are being studied, decongestive lymphatic therapy remains the cornerstone of management.

Conclusion

Family physicians are well-suited to provide care for most patients with cancer-related lymphedema and can have a meaningful impact on their lives by doing so. For patients with more complex or advanced cases, referral to a physician with expertise in lymphedema may be considered.

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Competing interests
None declared

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