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Exploring the value of prospective surveillance for cancer-related lymphoedema

Meadbh MacSweeney, Colette Cunningham, Joseph Harfouche, Conleth Murphy, Deirdre O Mahony

Introduction

LYMPHOEDEMA is a progressive condition characterised by regional swelling of a limb or body part because of disruption or damage to the lymphatic system. Cancer-related lymphoedema is when the lymphatic disruption occurs due to cancer treatment. Survivors of any type of cancer, in which treatment involves the lymph nodes, can be affected, including skin, gynaecologic, urologic, colorectal, and head and neck cancers. However, most research has involved breast cancer survivors and has specifically evaluated lymphoedema of the upper limb.[1] An understanding of the pathogenesis of lymphoedema and its consequences is key to appreciating the benefits of prospective surveillance, which can lead to lymphoedema detection at a subclinical level (before there is obvious swelling), facilitating effective early intervention and preventing the development of irreversible clinical lymphoedema. In this article, we aim to discuss cancer-related lymphoedema (CRL), describe its prevalence (acknowledging limitations in the existing prevalence data), pathophysiology, diagnosis and treatment and introduce our study exploring the value of prospective surveillance for CRL.

Background

Despite advances in cancer treatment, lifelong lymphoedema (limb swelling and the accompanying chronic inflammatory processes) affects approximately one in six individuals treated for cancer, although estimates of lymphoedema prevalence following cancer treatment vary widely depending on the diagnostic criteria used and the duration of follow-up.[2,3,4]

The Health Services Executive (HSE) published their national report on lymphoedema: 'A Model of Care for Ireland – A Working Group Report 2018'.[5] According to this report a conservative rate of 2.6 per 1,000 is used to estimate a prevalence in Ireland of approximately 12,380 cancer survivors with CRL, with an estimated incidence of approximately 1,490 new lymphoedema patients per year as the burden of the condition for health services in Ireland (Table 1). However, the executive summary highlights that accurate data is difficult to establish due to under-diagnosis, inaccurate recording and inadequate data collection on the conditions and services provided in both hospital and community.

Pathophysiology

It is important to note that describing the pathophysiology of lymphoedema as a mechanical insufficiency alone is likely simplistic. Lymphatic obstruction, inflammation, immune response, complement activation, wound healing, and fibrosis contribute to the development of lymphoedema.

Lymphoedema typically develops in two phases, an early reversible phase characterised by accumulation of excess extracellular fluid with no fibrosis (subclinical or mild lymphoedema), and a later chronic phase with irreversible intradermal fibrosis (chronic lymphoedema). There exists no gold standard for measuring lymphoedema. Furthermore, it is well established that choice of measurement method and applied criteria affect incidence estimates of chronic CRL. There are several measurement methods and even more diagnostic criteria.

The lack of a gold standard measure and definition of lymphoedema is in part because survivors can experience transient swelling in the first year after surgery. There is no accepted timeline for defining transient versus chronic CRL, some transient cases are misdiagnosed as chronic. Nevertheless, transient swelling during the first year after surgery has been found to be a strong predictor of chronic CRL, which is why prospective monitoring is warranted.

In the clinical context of cancer, the pathogenesis of lymphoedema ensues most typically from the modalities employed to stage and treat the cancer. More conservative surgery such as sentinel lymph node biopsy (SLNB) has reduced the risk of developing lymphoedema but a large cohort study of breast cancer patients has concluded that lymphoedema risk is also related to the other components of multimodal treatment including chemotherapy and radiation, weight and disease stage. There is still a 5.3% risk of developing lymphoedema following an SLNB.[6]

CRL staging

Classification of a lymphoedematous limb increasingly recognises Stage 0, which refers to a latent or sub-clinical condition where swelling is not evident despite impaired lymph transport.[7] It may exist months or years before overt oedema occurs (Stages I-III). Stage I represents an early accumulation of fluid relatively high in protein content (eg. in comparison with "venous" oedema) which subsides with limb elevation, pitting may occur. Stage II signifies that limb elevation alone rarely reduces tissue swelling and pitting is manifest. Late in Stage II, the limb may or may not pit as tissue fibrosis supervenes and stemmer sign is positive. Stage III encompasses lymphostatic elephantiasis, where pitting is absent and trophic skin changes such as acanthosis, fat deposits, and warty overgrowths develop.

Diagnosis

An accurate diagnosis of lymphoedema is essential for appropriate therapy. In most patients, it can be readily determined from the clinical history and physical examination. In other patients confounding conditions such as morbid obesity, venous insufficiency, occult trauma, and repeated infection may complicate the clinical picture. Moreover, in considering the basis of unilateral extremity lymphoedema, especially in adults, an occult visceral tumour obstructing or invading more proximal lymphatics needs to be considered.

Measures of lymphoedema include self-reported symptoms and

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Table1: Estimates of oncology-related lymphoedema, adapted from A Model of Care for Ireland – A Working Group Report 2018

Malignancy	Prevalence	Number of new cases of cancer per year	Estimated No of new lymphoedema patients
Breast	12-25%	2919	350-729
Gynaecological	33%	1076	355
Melanoma	20%	968	194
Prostate	10%	3364	336
Bladder	10-20%	438	44-88
Total		**8765**	**1490**

circumferential tape measurements as a minimum (provided they are completed with a non-stretch tape and at multiple points on each arm). A 2cm increase in circumference is commonly used to define lymphoedema. Volume displacement (VD) is considered the "gold standard" for lymphoedema diagnosis. Measurements obtained by VD have been shown to be reproducible, with an error rate of <1%. However, VD can be cumbersome and time consuming, limiting its clinical utility. Bioimpedance has emerged as a non-invasive method to measure limb volume. Bioimpedance involves passing a low-frequency electrical current through the extremity and measuring the opposition to flow of this current, also known as impedance. A cited advantage of bioimpedance is its ability to measure changes in extracellular fluid volume, which may more accurately reflect changes in lymphatic volume in particular early identification of subclinical extracellular fluid change.

Treatment

Combined decongestive therapy (CDT) is the accepted standard of care for CRL. This consists of manual lymphatic drainage (MLD), gradient compression bandaging (GCB), therapeutic exercises and skin care.

The clinical trial

The experienced clinical lymphoedema nurse therapist and educator, Ms Meadbh MacSweeney, recognised a void in this area and gathered parties interested in CRL and its impact on the patient, their community, and the Irish health service. This led to a collaboration between the Bon Secours Cork Cancer Centre, The Lymph Clinic and University College Cork's (UCC) School of Public Health, with the aim of establishing a new standard of care in Ireland.

Prior to the initiation of this collaborative project in 2021, prospective surveillance for cancer-related lymphoedema had not been implemented in lymphoedema services in the Republic of Ireland.

While there is research investigating the impact on the quality of life of those with breast cancer-related lymphoedema, few studies have looked at the impact of lymphoedema on other cancer subtypes, particularly poor prognosis cancers. With the generous support of a Breakthrough Cancer Research (BCR) grant, this study has been able to open and, so far, recruit patients with melanoma, sarcoma, and cervical cancer at risk of CRL, as well as those with breast cancer. This study is unique as it is open to a broader group of 'at risk' patients than many previous CRL studies.

Study design

The clinical trial has been approved by both the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) and the Bon Secours Hospital Group Ethics Committee. The study is open to patients from the Bon Secours Hospital as well as patients referred by collaborating specialists in hospitals from the HSE South/South West Hospital Group. At-risk patients identified from the local/regional cancer multidisciplinary teams are furnished with a patient information leaflet. Patients at risk of lymphoedema will be recruited prior to their first therapeutic intervention.

The PeriKit® is a novel kit to perform circumferential measurements. This has been designed based on several years of practices and research. The methodology to use the device is Dr Joseph Harfouche's method, based for the first time on a fixed bony landmark called the reference point. The PeriKit® is composed of two parts: PeriBase and PeriTape. The PeriBase offers a high degree of precision in the location of the place of the measurement, reducing inter-assessor variability. The PeriTape gives a high degree of precision in the circumference measurement. Used together they give the ability to measure any body segments with an accuracy of few millimetres. That is why the PeriKit® insures repeatability and reproducibility between intra- and inter-assessors. Thanks to the PeriKit® we can remove definitively the major error factors and bias from the measurements in the assessments, improving the validity of studies.

Limb range of motion (ROM) and Bioimpedance Spectroscopy (BIS) using a SOZO BIS device are also recorded. In addition, patients complete Quality of Life (QOL) assessments so that we may understand the impact of cancer and its treatment on patients and their families. Subsequent quarterly scans and measurements will be undertaken up to a period of 24 months. Education on early detection of lymphoedema and risk reduction techniques will be provided to all patients at The Lymph Clinic on their subsequent visit.

An important aspect of this study is the qualitative research using one-to-one semi-structured interviews which will be audiotaped and then transcribed. Purposive sampling will be utilized to obtain a subset of patients from the overall cohorts who represent a diversity of tumour types, gender, age, and treatment type. The in-depth interviews will focus on quality-of-life issues as well as patients' perception regarding the value of the interventions, their impact and what it means to them. There will be scope in the interview for patients to identify issues relating to lymphoedema that are perceived by them to be important in their care. Qualitative data will be analysed using thematic analysis.

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Summary

The call to integrate prospective surveillance for lymphoedema into cancer care pathways is building momentum to enable early intervention and prevent the progression of the condition.[8] Chronic cancer-related lymphoedema requires lifelong management, prospective surveillance programmes with routine measurements and early management when subclinical lymphoedema is identified may be a model for preventing chronic lymphoedema.[1] The National Cancer Strategy 2017-2026 highlights the need for management of lymphoedema.[9] Despite this, prospective surveillance is not yet current practice within the Irish healthcare system, either public or private. Consequently, there is an opportunity for this research to introduce early detection as a potential risk-reduction factor to the development of secondary lymphoedema and examine the value to patient, community, and health service.[10]

Meadbh Mac Sweeney is Clinic Director at The Lymph Clinic (TLC) based at the Cork Clinic, Western Road, Cork; **Colette Cunningham** is a Lecturer in Global Public Health at University College Cork; **Joseph Harfouche** is a Doctor in physiotherapy and inventor of the Perikit, Chirec, Delta Hospital, Brussels, Belgium; and **Conleth Murphy** and **Deirdre O Mahony** are consultant medical oncologists at the Bon Secours Cork Cancer Centre

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