

CAPITALISING ON THE MOMENTUM THROUGH COLLABORATION

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Lymphoedema (LE) is a dreaded condition. It is debilitating, chronic, and progressive, and is most commonly the result of cancer treatment (i.e. the surgical removal of lymph nodes or disruption to lymphatic pathways) in industrialised countries, or of filariasis in lesser developed countries. Lymphoedema is associated with significant medical, economic, and quality of life consequences, and over the last decade, LE awareness has increased as a result of the grass-roots efforts of patients, advocacy groups and LE specialists. In 2009, there is clear evidence that clinicians, investigators, organisations, and other stakeholders have taken collective notice of these efforts and are working together to advance the field.

One indicator is the body of literature pertaining to LE which has increased markedly over the last decade both in volume and in quality. A PubMed keyword search revealed a more than 50% increase in returned citations for 2008 than for 1990 when using the keyword 'lymphedema' (Figure 1). The increase is even more dramatic for the more limited-search on 'lymphedema AND cancer', with a nearly three-fold increase in number of retrieved citations for the same time period. Though there was fluctuation between annual estimates, the increasing trend remains clear and is likely to continue in the coming decades.

Although, to date, LE studies have focused primarily on patients with breast cancer following axillary lymph node dissection, essentially any surgical treatment that disrupts the lymphatic system results in a lifetime risk of LE, regardless of the malignancy. Over the last decade, LE

has increasingly been recognised and documented by clinicians as occurring as a result of treatment for many other malignancies including melanoma, sarcoma, gynaecologic, genitourinary, and head/neck cancer. Although few in number, prospective studies examining the incidence of lower extremity LE following inguino-femoral and/or deep pelvic lymph node dissection for melanoma, gynecologic, genitourinary, and sarcoma have reported an incidence of 10–40% (Bergman et al, 2002; Henningsohn et al, 2002; Lawton et al, 2002; Billings et al, 2004). As with studies in breast cancer patients, studies that involved the shortest follow-up (<12 months) showed the lowest incidence of LE (Lawton et al, 2002; Fujiwara et al, 2003), whereas studies that involved the longest follow-up showed the highest incidence (Chatani et al, 1998; Bergmark et al, 2002). Given that prevention and management of early LE is currently the most effective treatment to enhance the quality of surgical oncology care, LE measurement and symptom assessment should become standard practice during surveillance evaluation.

Sentinel lymph node (SLN) biopsy has been the single most significant advancement in the field of surgical oncology over the last 20 years. Initially

described by Dr Morton in 1992 (Morton et al, 1992), SLN biopsy is a highly accurate, minimally invasive surgical procedure that is based on the theory that the lymphatic metastases associated with various malignancies follow an orderly progressive route through afferent lymphatic channels from the primary tumour to a sentry lymph node (designated the 'sentinel lymph node'), before spreading into other regional ('nonsentinel') lymph nodes. It has now been well established that SLN biopsy is a reliable technique for identifying micrometastatic disease in regional lymph node basins that are clinically negative for a variety of cancers. For patients with negative SLN, no further surgical therapy is recommended, which spares patients from undergoing complete lymph node dissections. It was hoped that novel surgical techniques such as sentinel lymph node biopsy would largely eliminate LE as a post-surgical complication. Unfortunately, recent studies have shown that a fraction of cancer patients (6–8% in most recent reports) continue to develop LE following the less invasive surgical technique (Wilke et al, 2006; Lucci et al, 2007).

Several large prospective cohort studies of breast cancer patients have provided much needed information on the natural history and risk factors associated with this condition (Armer and Stewart, 2005; Wilke et al, 2006; Paskett et al, 2007). For example, it is now clear that the development (or severity) of LE is not merely a function of the extent of surgery. In fact, multiple factors have been determined to increase risk, including age, body mass index (BMI), postoperative infection, and whether radiotherapy is part of the treatment regimen. Similarly, advancements have been made in molecular research with the identification of gene mutations and lymphatic endothelium-specific markers that control

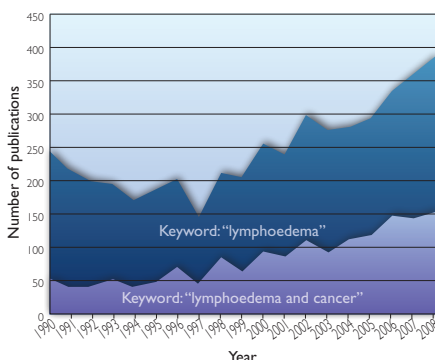


Figure 1. Publications returned in keyword searches of PubMed from 1990–2008.

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lymphatic growth and function (Ferrell and Finegold, 2008). Genetic mouse models are now available which have provided the framework for examining lymphatic development and pathways leading to hereditary LE. It is the hope that these genetic studies of inherited LE will provide a starting point for understanding genetic risk factors for secondary LE (Nakamura and Rockson, 2008).

The true prevalence and incidence of LE have been difficult to elucidate, and are likely to be underestimated due to the lack of consensus pertaining to clinical definitions and inaccurate methods of limb assessment. The development and deployment of new technologies has been promising for the field in that more accurate devices with standardised assessment techniques are already available. For example, opto-electronic perometry makes use of infrared imaging to map the majority of the surface of the limb. From the mapping, volume measures are subsequently calculated, and when compared with contralateral limb measures at baseline and follow-up, changes in limb volume are documented in the form of clinically familiar, standardised volume measures. Multi-frequency bioimpedance spectroscopy is another novel technique for assessing change in limb volume. By assessing changes in electrical resistance from interstitial fluid build-up, changes in limb volume are calculated with minimal burden to the patients. Other types of evaluation that may continue to be more practical for clinical practice, include circumference measurements combined with symptom, function, and quality of life assessment.

While technological advancements are important to research efforts, equally important to making progress in the field of LE is the increased interest and involvement of clinicians, investigators, and other stakeholders. Fortunately, partnerships such as the International Lymphoedema Framework (ILF) in the United Kingdom (founded in 2002 and directed by Professor Christine Moffatt, CBE) and the American Lymphedema Framework Project (ALFP) which was established in 2008 under the direction of Drs Jane Armer, PhD, RN, FAAN and Joe Feldman, MD, are already actively working

to establish collaborations among clinicians, researchers, healthcare organisations, support groups, care-givers, and patients. Reflecting the reach of this debilitating condition, prominent groups such as the World Health Organization (WHO) and the Global Programme to Eliminate Lymphatic Filariasis (GPELF) have joined international and national lymphology groups to establish partnerships to develop internationally agreed-upon standards of best practice for a variety of service models. The recently established international advisory board of the ILF will meet for the first time this month, and its formation will help maintain the perspective of LE as a multinational health issue that afflicts patients worldwide. Recent collaborations in the US include the first stakeholders meeting of the AFLP held last month in Chicago, Illinois. Multiple perspectives from more than seventy LE stakeholders including patients (15%), therapists (26%), physicians (9%), industry representatives (17%), researchers (16%), nurses (4%), and educators (3%) were brought together in an 'Open-Space' meeting to collectively establish priority issues and recommend actions to move the field forward.

In the era of evidence-based medicine, objective, accurate, and reliable measures, as well as standardised clinical definitions and guidelines for best practice for LE are critical, and will be increasingly integral to outcome-driven advancements. The development of prognostic genetic factors which may lead to individualised risk-reduction practices, and a better understanding of the risk factors contributing to LE could lead to profile-specific treatment modalities. There is reason for optimism amidst the LE challenges that are faced every day by clinicians and patients alike. Grass-roots efforts of advocacy groups composed of many patients and specialists across the globe have been valuable in increasing awareness of LE, and in drawing needed attention to our collective cause. The momentum of these collaborations, along with those of clinicians and investigators has led to promising advances in the field.

More information about the ALFP and ILF can be found at: www.alfp.org and intl.org. **JL**

References

- Armer JM, Stewart BR (2005) A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymph Res Biol* 3(4): 208–17
- Bergmark K, Avall-Lundqvist E, Dickman PW, et al (2002) Patient-rating of distressful symptoms after treatment for early cervical cancer. *Acta Obstet Gynecol Scand* 81(5): 443–50
- Billings SD, McKenney JK, Folpe AL, et al (2004) Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. *Am J Surg Pathol* 28(6): 781–8
- Chatani M, Nose T, Masaki N, Inoue T (1998) Adjuvant radiotherapy after radical hysterectomy of the cervical cancer. Prognostic factors and complications. *Strahlenther Onkol* 174(10): 504–9
- Ferrell RE, Finegold DN (2008) Research perspectives in inherited lymphatic disease: an update. *Ann N Y Acad Sci* 1131: 134–9
- Fujiwara K, Kigawa J, Hasegawa K, et al (2003) Effect of simple omentoplasty and omentopexy in the prevention of complications after pelvic lymphadenectomy. *Int J Gynecol Cancer* 13(1): 61–6
- Henningsohn L, Wijkstrom H, Dickman PW, et al (2002) Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol* 62(2): 215–25
- Lawton G, Rasque H, Ariyan S (2002) Preservation of muscle fascia to decrease lymphedema after complete axillary and ilioinguinofemoral lymphadenectomy for melanoma. *J Am Coll Surg* 195(3): 339–51
- Lucci A, McCall LM, Beitsch PD, et al (2007) Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol* 25(24): 3657–63
- Morton DL, Wen DR, Wong JH, et al (1992) Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 127(4): 392–9
- Nakamura K, Rockson SG (2008) Molecular targets for therapeutic lymphangiogenesis in lymphatic dysfunction and disease. *Lymph Res Biol* 6(3–4): 181–9
- Paskett ED, Naughton MJ, McCoy TP, et al (2007) The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. *Cancer Epidemiol Biomarkers Prev* 16(4): 775–82
- Wilke LG, McCall LM, Posther KE, et al (2006) Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. *Ann Surg Oncol* 13(4): 491–500