

Use of microsurgery for the prevention and treatment of cancer-related lymphedema

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SUMMARY

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Introduction

Cancer-related lymphedema is a complication caused by dysfunction of the lymphatic system following certain oncologic treatments or by the cancer itself, the most common of which are breast, gynecological, skin and urogenital cancers. It can occur after surgical treatment of cancer such as lymph node dissection or sentinel node biopsy, but also following radiotherapy treatments. The main manifestations are swelling of the affected limb or area, which may be accompanied by a feeling of heaviness, stiffness or pain and a decrease in mobility. Lymphedema can also induce physical morbidity and cause psychological distress in patients, which can significantly affect their social relationships and quality of life. In addition, individuals are at greater risk of experiencing episodes of cellulitis and lymphangitis, which can increase the frequency of hospitalization and the costs associated with treatment.

The current treatment offered to people with lymphedema is complex decongestive therapy. This involves, among other things, manual drainage and the wearing of compression garments, which are generally necessary for the rest of the patient's life. Although this therapy can, in some cases, reduce and maintain a reduced volume of the affected limb, it does not restore the damaged lymphatic network.

Microsurgery could be an alternative to restore the damaged lymphatic network and thus prevent and improve the symptoms of people with cancer-related lymphedema. Among these microsurgeries is Lymphatic Microsurgical Preventing Healing Approach (LYMPHA). This is performed at the same time as the oncology surgery, before the onset of lymphedema. Lymphaticovenous anastomosis and vascularized lymph node transfer are, for their part, therapeutic microsurgeries performed on patients with lymphedema.

Background

Given the potential benefits of LYMPHA, lymphaticovenous anastomosis, and vascularized lymph node transfer for the prevention and treatment of cancer-related lymphedema, INESSS was mandated to evaluate the clinical relevance of these microsurgeries in Quebec health care institutions and, if appropriate, to make recommendations regarding the organization of this service offering in Quebec.

Methodology

A systematic review of data from the literature was conducted to document the efficacy and safety of various microsurgeries. The literature considered includes cancer patients of all types and stages who have undergone microsurgery to prevent or cure lymphedema. Stakeholder consultations, including clinical experts as well as patients,

were conducted. Clinical and administrative data were also analyzed to obtain a portrait of the problem in Quebec, to evaluate the costs of microsurgery and the budgetary impact that microsurgery could have if it were implemented in our health care system. All of the data were integrated to produce findings to which a level of evidence was attached. These findings, along with proposed recommendations, were submitted to INESSS *Comité délibératif permanent — Modes d'intervention en santé* (standing deliberative committee on health care interventions) for deliberation in order to formulate the final recommendations.

Findings

The integration of scientific, contextual, and experiential data resulted in the following findings:

Health needs

- Cancer-related lymphedema is relatively common and occurs primarily following surgical treatment of cancer (lymph node dissection or sentinel node biopsy), but also following radiation treatments.
- The majority of cancer-related lymphedema occurs within 2 years of cancer surgery, but clinical experience has shown that some patients develop symptoms up to 20 years later.
- Lymphedema is a pervasive and significant source of anxiety for patients. Unlike cancer, patients have no hope of recovery from lymphedema.
- The number of people who may have lymphedema in Quebec is difficult to quantify. According to the literature, the risk of developing lymphedema following axillary dissection or radiation therapy for breast cancer is estimated to be 15 %, which could represent between 635 and 1074 new cases of lymphedema in Quebec annually (breast cancer-related lymphedema only). Changes in surgical practices for the treatment of breast cancer, such as the advent of sentinel node biopsy, have tended to decrease the number of potential new cases of lymphedema in recent years.

Management

- Management of patients with cancer-related lymphedema appears to be compromised by a lack of knowledge among health care professionals and other participants, limited access to information, and the absence of a care pathway for this condition.
- Complex decongestive therapy is the current treatment offered to patients with early to advanced cancer-related lymphedema. It represents a significant burden for patients.

- Access to complex decongestive therapy is limited due to a limited number of certified therapists performing this procedure. Most of them work in private clinics, which requires a significant financial investment from the patient.
- Patient compliance with complex decongestive therapy appears to be variable due to the large amount of daily care. Self-drainage, compression garments, skin care and exercise occupy a large part of the patient's day.
- Complex decongestive therapy could maintain a reduced volume of the affected limb without restoring the injured lymphatic network.
- Microsurgeries could be an alternative, or an adjunct, to prevent or improve symptoms in some patients with cancer-related lymphedema by restoring the injured lymphatic network.

Status of microsurgery practice in Quebec

- Currently, no facilities offer LYMPHA to prevent cancer-related lymphedema.
- Two Montreal health care facilities offer microsurgeries to treat patients with lymphedema using the lymphaticovenous anastomosis or vascularized lymph node transfer.
- A third facility is currently developing a project to acquire the necessary equipment to perform LYMPHA, lymphaticovenous anastomosis and vascularized lymph node transfer.
- Three plastic surgeons are subspecialized in microsurgeries for the prevention and/or treatment of lymphedema. The number of patients currently treated remains minimal.
- According to the experts consulted, the provision of therapeutic microsurgeries services should be concentrated in certain specialized centres having the necessary expertise and equipment.
- Considering that the practice of lymph node dissections exists in a large number of centres throughout Quebec and the difficulty of selecting the patients who could most benefit from it, it would be difficult to consider offering LYMPHA to all patients potentially at risk of developing lymphedema.
- The addition of LYMPHA to cancer patients could increase operative time and lengthen surgery waiting time for cancer patients and even other populations requiring surgery.

Assessment of the level of scientific evidence

- Although there are a few studies on the subject, the level of evidence associated with the evaluation of the efficacy and safety of microsurgery for the prevention or treatment of breast cancer-associated lymphedema is considered low. Several

methodological limitations and variability make generalizations of the available data extremely difficult.

- There are insufficient available data to evaluate the efficacy of microsurgery for lymphedema in other cancers.
- For these reasons, the following findings relate only to microsurgery for the prevention and treatment of breast cancer-related lymphedema.

Efficacy and safety

- LYMPHA, the only procedure that can prevent breast cancer-related lymphedema, appears to be an effective technique that decreases the risk of developing lymphedema following axillary dissection in breast cancer treatment.
- Lymphaticovenous anastomosis and vascularized lymph node transfer appear to be effective techniques for the treatment of breast cancer-related lymphedema by:
 - decreasing the volume of the affected limb;
 - reducing the annual number of episodes of cellulitis and lymphangitis;
 - improving patients' quality of life and symptoms;
 - reducing or discontinuing the use of compression garments.
- All three microsurgeries have few side effects. The only major complication reported in a limited number of patients is the development of lymphedema at the donor site following the lymph node transfer technique. No major complications have been reported with LYMPHA or lymphaticovenous anastomosis.
- According to the experts consulted, the effectiveness of microsurgeries is dependent on patient selection. The development of selection criteria, although not clearly explicit in the selected literature, is necessary.
- Very few data are available regarding the long-term benefits of microsurgeries for the treatment of lymphedema.
- Most authors of recent publications recommend microsurgeries for the treatment of lymphedema (very low to moderate guideline quality).
- Seven phase III randomized clinical trials are underway to evaluate LYMPHA and lymphaticovenous anastomosis for the prevention and treatment of breast cancer-related lymphedema (last data collection: August 2022 for 3 of 7 studies).

Efficiency and cost Analysis

- Analysis of the economic evaluations identified in the literature suggests that microsurgeries for the prevention and treatment of breast cancer-related lymphedema would be cost-effective compared with complex decongestive therapy.

- Given the uncertainty associated with the clinical data, the methodological weaknesses of the identified studies, and the transferability issues observed, an efficiency analysis could not be performed.
- A cost analysis shows that LYMPHA, lymphaticovenous anastomosis and vascularized lymph node transfer could result in total costs of \$5149, \$9956 and \$15745 per patient in Quebec hospitals, respectively.
- Considering that approximately 25 % of people with lymphedema could be candidates for microsurgery (expert opinion), and that the number of potential new cases of breast cancer-related lymphedema in 2019 is estimated to be between 635 and 1,074 patients, the gross budgetary impact to treat these new candidates could be between \$1.4 million and \$3.8 million over 1 year. This estimate is highly hypothetical and does not take into account the purchase and maintenance of equipment, all cumulative lymphedema cases from previous years, and the limited capacity of technical facilities. In addition, the estimate does not take into account the potential savings that could be generated by a decrease in the number of compression garments reimbursed by the RAMQ (Régie de l'assurance maladie du Québec) assistance program and a decrease in the number of hospitalizations related to episodes of cellulitis in lymphedema patients.

INESSS position and recommendations

Considering:

- ✓ the important health needs of people with lymphedema related to all types of cancer in Quebec;
- ✓ the promise of microsurgeries for the prevention and treatment of lymphedema related specifically to breast cancer, although the evidence currently available does not allow concluding with certainty as to the clinical benefit of these microsurgeries compared to complex decongestive therapy;
- ✓ the limited service offer already in place in some centres in Quebec and the quality of clinical studies currently underway that will complete the level of scientific evidence.

INESSS supports the development of therapeutic microsurgeries, i.e. lymphaticovenous anastomosis and vascularized lymph node transfer, for the treatment of lymphedema specifically related to breast cancer.

In support of this position, INESSS recommends that:

- R1.** Therapeutic microsurgeries services should be offered in a limited number of specialized centres to support the gradual development of expertise, maximize clinical benefit to patients, and optimize the use of available resources.

- R2.** Designated specialized centres offering microsurgeries services should collaborate to establish common clinical guidelines, including patient selection criteria, while seeking to promote equitable access to patients from different regions of Quebec. These criteria should be disseminated to inform and equip health care professionals, organizations, patients and caregivers.
- R3.** The decision to perform a microsurgery should be based on a process of shared decision-making and informed consent by the patient, including an explanation of the current level of evidence regarding the efficacy as well as the risks directly associated with performing the microsurgery.
- R4.** Specialized centres offering microsurgeries services should collaborate to collect data in a standardized manner that will allow for the development of knowledge and evidence in real-world care settings in Quebec. The data collected should include the type of procedure performed, the clinical characteristics of the patient, and the clinical outcomes observed, including those deemed important to patients (e.g., quality of life).

Considering:

- ✓ the presence of significant organizational issues, the difficulty in targeting patients who might benefit from preventive microsurgery, and the anticipated decrease in need over time.

INESSS does not support the development of a systematized and expanded practice of LYMPHA for the prevention of breast cancer-related lymphedema.

Other considerations in the management of lymphedema:

- The long-term effectiveness of complex decongestive therapy has never been comprehensively evaluated. According to the publication of a recommendation by the INESSS in 2011, only compression bandages and the wearing of compression garments seem to significantly reduce or prevent the aggravation of lymphedema. Considering the available data, the uncertainties that persist, and the lack of knowledge and information reported by patients, it may be relevant to:
 - conduct an evaluation of the long-term effectiveness of complex decongestive therapy based on the best available data;
 - develop and make available information and teaching tools related to lymphedema and its management. These tools should target health care providers as well as patients and their families;
 - educate clinicians about the importance of informing patients of the risks of developing lymphedema at the time cancer surgery or radiation therapy is proposed;

- advocate for an early identification process for lymphedema following oncology surgery.
- Appropriate use of RAMQ lymphedema diagnostic codes and/or the addition of fee-for-service billing codes for microsurgeries could help to identify affected individuals, track their care trajectory, monitor practices and analyze the costs associated with the various treatments.

Updating the Recommendations

The relevance of updating this advisory will be evaluated and determined based on the contribution of new data in support of any of the dimensions addressed in this advisory, particularly the publication of the results of ongoing clinical trials and the collection of data in the Quebec context.

*Institut national
d'excellence en santé
et en services sociaux*

Québec 

Siège social

2535, boulevard Laurier, 5^e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12^e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563

inesss.qc.ca

