Summary
Sentinel Lymph Node Biopsy in Breast Cancer Treatment: Efficacy and Safety
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Summary of the report prepared by
Raymonde M.-H. Mayot et Cathy Gosselin
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Introduction

In Canada, breast cancer is the most common type of cancer in women (27.6% of all reported cases). The Canadian Cancer Society estimates that approximately 23,400 new breast cancer cases occurred in the country in 2011, including 6200 in Québec. Breast cancer is also the second leading cause of cancer death among women (14.4%), after lung cancer.

Currently, breast cancer is often diagnosed at an early stage with a low risk for lymph node metastasis, a major prognostic factor for the course of the disease. Since the mid-1990s, sentinel lymph node biopsy (SLNB) has been proposed as an alternative to axillary lymph node dissection (ALND), the standard tumour staging procedure for this type of cancer. Given that SLNB is a less invasive surgical technique than ALND, its use has spread quickly, even before the publication of long-term efficacy outcomes from major randomized controlled trials. In early-stage cancer without clinically detectable adenopathy, SLNB is now proposed as the single axillary surgery procedure when the sentinel lymph nodes prove to be free of metastasis at anatomical pathology examination (pSLN-). In the case of positive sentinel lymph nodes (pSLN+), supplemental ALND is usually required.

In the context of breast cancer management in Québec, the Comité de l'évolution des pratiques en oncologie (CEPO) had questions regarding the efficacy, associated morbidity and safety of SLNB as part of breast cancer treatment. This committee asked the Unité d'évaluation en oncologie of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), now the Institut national d'excellence en santé et en services sociaux (INESSS), to examine currently available evidence on these issues.

Research Method

This report addresses only patients with early-stage breast cancer without clinically detectable adenopathy. It consists of a systematic literature review designed primarily to compare patients who underwent SLNB alone versus ALND (alone or preceded by SLNB), in terms of (i) overall survival and disease-free survival, 5 or more years after axillary surgery; and (ii) frequency of axillary, regional, local and distant recurrence, and frequency of de novo tumours, 2 or more years after axillary surgery.

This review also compared SLNB alone versus ALND (alone or preceded by SLNB), regardless of the anatomical pathology status of the axillary lymph nodes, in terms of (i) induced morbidity (secondary lymphedema in the arm, motor impairments in the arm and shoulder, and sensory impairments); (ii) quality-of-life effects; and (iii) frequency of complications emerging within 30 days of axillary surgery (allergic or other reactions related to the vital blue dye used to detect sentinel lymph nodes, along with seromas, lymphoceles, surgical wound infections and hematomas).

This assessment covers the scientific literature published from December 2003 to June 2011 (retrieved from several databases) and updates the results found in the assessment report produced by the Medical Services Advisory Committee (MSAC) (Australia). It includes systematic reviews, randomized controlled trials (RCTs), non randomized comparative studies, case series (for SLNB alone) and case reports (for complications following SLNB alone). Two evaluators selected the studies and then independently appraised the data. The work of classifying the studies according to their level of evidence and of analyzing the methodological quality of the systematic reviews and the RCTs was carried out in parallel.
**Results**

This assessment pools the results of 7 systematic reviews, 9 randomized controlled trials, 23 observational cohort studies, 24 case series and 4 case reports.

**Survival**

**SLNB (+ALND only in the presence of sentinel lymph node metastasis) versus SLNB+ALND**

- Three RCTs did not show a statistically significant survival difference between groups of patients treated with SLNB (followed by ALND in the case of positive sentinel lymph nodes) versus SLNB systematically followed by ALND. In the 3 RCTs, between 30.0% and 36.8% of the patients in the SLNB group underwent ALND, given that they presented with sentinel lymph node metastasis.

- The 3 RCTs reported 5-year overall survival rates of between 94.8% and 98.4% in the SLNB group and between 95.5% and 97.2% in the SLNB+ALND group. The 5-year disease-free survival rate ranged from 87.6% to 94.5% in the SLNB group, and from 88.9% to 89.9% in the SLNB+ALND group.

- The Milan RCT [Veronesi et al., 2010] reported 10-year overall survival rates of 93.5% and 89.7% in the SLNB and SLNB+ALND groups respectively. The estimated 10-year disease-free survival rate was 89.9% in the SLNB group and 88.8% in the SLNB+ALND group.

**SLNB alone versus SLNB+ALND (pSLN- patients)**

- An RCT and a cohort study compared the 5-year and 8-year overall survival and disease-free survival of pSLN- patients treated with SLNB alone versus SLNB+ALND; neither found a statistically significant survival difference between the two groups.

- In the North American NSABP B-32 trial [Krag et al., 2010], a comparison of the findings between the groups of SLNB alone and SLNB+ALND in pSLN- patients showed 5-year overall survival and disease-free survival rates of 95.0% versus 96.4% and 88.6% versus 89.0% respectively, accounting for a difference of less than 2% for a previously calculated sample size. At 8 years, survival was respectively 90.3% versus 91.8% (overall) and 81.5% versus 82.4% (disease-free).

- The cohort study led by Kim et al. [2010] estimated the 5-year overall survival rate of pSLN- patients to be 98.4% in the SLNB group and 98.7% in the SLNB+ALND group. The 5-year disease-free survival rate was 95.2% in both treatment groups.

**SLNB alone (pSLN- patients)**

- In the case series, the 5-year overall survival was estimated to range from 92% to 99%; the estimated 5-year disease-free survival ranged from 90% to 96%.

**Frequency of recurrence and de novo tumours**

**SLNB (+ALND only in cases of sentinel lymph node metastasis) versus SLNB+ALND**

- In the RCTs, the frequency of axillary recurrence was uncommon (≤ 0.8%), regardless of the treatment, for a median follow-up period of up to 102 months. None demonstrated a difference in the frequency of axillary, local or distant recurrence between the patients treated with SLNB (+ALND in the case of positive sentinel lymph nodes) or with SLNB+ALND. The pre-recurrence remission periods appeared to be similar.

**SLNB alone versus SLNB+ALND (pSLN- patients)**

- After an 8-year follow-up, the NSABP B-32 trial [Krag et al., 2010] did not show a difference in the remission period before a regional, local or distant recurrence in pSLN- patients who had undergone SLNB alone versus SLNB+ALND. The frequency of axillary recurrence was less than or equal to 0.4% in both groups.
• No cohort study showed a difference in the frequency of axillary, local or distant recurrence in pSLN- patients who had undergone SLNB alone versus SLNB+ALND. The frequency of isolated axillary recurrence, where mentioned, varied from 0.04% to 2.7% for a maximum follow-up period of 71.5 months; the frequency of total axillary recurrence ranged from 0% to 3.6% for a maximum follow-up period of 60 months. In the SLNB group, axillary recurrence took place between 3 and 40 months.

**SLNB alone (pSLN- patients)**

• According to a meta-analysis, the frequency of axillary recurrence in pSLN- patients who underwent SLNB alone was on the order of 0.3% (with a median remission of 20 months).

• In the new case series, the median frequency of axillary recurrence was 0.8% (with a range from 0% to 2.8%). The median remission was 23 months (with a range from 2 to 108 months).

**Lymphedema**

• The systematic reviews concluded that lymphedema-related morbidity was lower among patients who had undergone SLNB alone than among those who had undergone ALND (preceded or not by SLNB).

• Objective assessment: 5 RCTs (Milan, NSABP B-32, Sentinella-GIVOM, Cambridge, and SNAC) showed that, up to 12 months after surgery, lymphedema was more frequent or arm volume increase was greater in patients who had undergone ALND than in those who had had SLNB. The NSABP B-32 trial presented results up to 36 months after surgery; the difference was always significantly in favour of SLNB. The results of 5 cohort studies, including a major study that conducted a 5-year post-surgery follow-up, corroborated those of the RCTs.

• Subjective assessment: In the RCTs, ALND patients reported more frequent lymphedema or increased swelling in the ipsilateral arm than did SLNB patients at 6 months, 12 months (ACOSOG Z0011, ALMANAC and SNAC trials) and 18 months (ALMANAC trial) after surgery. All the 5 cohort studies also showed significant differences for follow-up periods ranging from 6 to 60 months.

• According to 2 meta-analyses, the risk for lymphedema may be 3 times greater after ALND (alone or preceded by SLNB) than after SLNB.

• According to a third meta-analysis, the prevalence of lymphedema varied from 6.0% to 14.0%, 12 or more months after surgery in patients who had SLNB alone. After a 5-year follow-up, lymphedema was still present in 6.8% of the patients.

**Motor impairments of the arm and shoulder**

• Two systematic reviews concluded that motor impairments were less frequent or less severe after SLNB than after ALND, but a third review concluded that there was no long-term (12 or more months) difference between the groups.

• Three RCTs showed that limitations in shoulder motion, measured objectively, were significantly greater after ALND (preceded or not by SLNB) than after SLNB alone, at 1 month (ALMANAC), 6 months (NSABP B-32) and 12 months (Cambridge) after surgery. According to the ALMANAC trial, the difference between the treatment groups had disappeared by 3 months after surgery.

• Three RCTs showed a difference in limitations in arm and/or shoulder motion, measured subjectively, in favour of SLNB, at 1 month, 3 months (ALMANAC), 6 months (Sentinella-GIVOM and Milan) and 12 months (Milan) after surgery. According to the ALMANAC trial, the difference between the treatment groups had disappeared by 6 months after surgery.

• The cohort studies showed differences in limitations in shoulder motion, measured objectively, in favour of SLNB at 6 months, 18 months (1 study), 30 months (1 study) and even 36 months (1 retrospective study) after axillary surgery.
Motor impairments induced by axillary surgery did not differ between patients treated with SLNB+ALND and patients treated with ALND alone.

Sensory impairments
The presence of sensory impairments was most often reported in subjective assessments. These mostly involved pain in the axilla and arm, numbness, arm paresthesia or self-reported sensory disturbances.

- The systematic reviews concluded that there was a significant difference in sensory impairments, which were less common after SLNB alone than after ALND (preceded or not by SLNB), a difference that persisted several months after surgery.
- Paresthesias in the ipsilateral arm were less common or less severe after SLNB alone compared with SLNB+ALND, or compared with ALND alone, by the first weeks after surgery in the comparative trials whether randomized or not. The difference remained statistically significant well beyond 12 months.
- Pain was significantly less common in the case of SLNB alone in the first 6 months following surgery, then the difference disappeared more or less quickly depending on the study; it remained significant beyond 12 months in the cohort studies.

Quality of life
- The RCTs used different questionnaires and follow-up periods to evaluate quality of life.
- Depending on the study, the questionnaire and the aspect evaluated, the quality of life of patients treated with SLNB was either similar to or better than that of patients treated with ALND.
- Generally, patients treated with SLNB have a better overall quality of life than those treated with ALND.
- Quality-of-life differences observed in the treatment groups were especially pronounced in the first weeks or months following surgery during which a greater decrease in quality of life was observed among patients treated with ALND, after which the differences between the groups lessened and generally disappeared.

Safety
- SLNB alone confers an advantage over SLNB+ALND, given its lower frequency of surgical wound infections and seromas in the 30 days following axillary surgery. The frequency of hematomas was similar in both treatments.
- The use of vital blue dye to detect sentinel lymph nodes is associated with a risk of allergic reaction on the order of 1%, with effects ranging from uncomplicated hives to anaphylactic shock; no deaths have been reported following allergic reactions.
- The use of vital blue dye is also associated with the risk of skin staining; other types of complications are uncommon but real.

Conclusions
After analyzing the available literature, INESSS concludes that, in patients with early-stage breast cancer, without clinically detectable adenopathy, the use of axillary lymph node dissection following sentinel lymph node biopsy is not necessary when patients do not present with lymph node metastasis at the definitive anatomical pathology examination (pSLN-).
Compared with ALND:

- SLNB is a clinically effective procedure, given that
  - 5-year survival is similar for both types of surgical approaches,
  - axillary recurrence following SLNB is an uncommon event,
  - the risk for axillary recurrence following SLNB is comparable to that attributed to ALND, taking into account the limitations of the available studies,
  - however, no conclusion can be drawn about the risk for local and distant recurrences following SLNB, owing to insufficient data;
- SLNB causes less frequent and less severe morbidity than ALND, that is,
  - it significantly reduces the frequency and severity of secondary lymphedema, although its associated risk is on the order of 7%,
  - it induces fewer motor and sensory impairments,
  - it offers a better overall quality of life to patients in the first weeks or months after surgery;
- SLNB is a safe procedure because
  - it results in fewer surgical wound infections and seromas, and no greater frequency of hematomas, in the first 4 weeks following the surgical procedure;
- SLNB is a potential, although uncommon, source of allergic complications or other types of reactions caused by the vital blue dyes sometimes used for detecting sentinel lymph nodes, requiring vigilance on the part of clinicians and healthcare staff, along with patient information.