

# SUMMARY

## SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER TREATMENT: TECHNICAL ASPECTS

### Introduction

In Québec, about 6000 women will be diagnosed with breast cancer in 2009. Currently, with population screening mammography and improved imaging techniques, breast cancer is diagnosed at earlier stages and with a lower risk of lymph node invasion, the most significant prognostic factor in early-stage breast cancer. The extent of lymphatic involvement used to be routinely determined by axillary lymph node dissection, also called axillary dissection, a surgical technique that involves removing 15 or so lymph nodes from the axilla for anatomical pathology examination. This technique is associated with non-negligible postoperative morbidity, however.

A less invasive option than axillary dissection currently exists: sentinel lymph node biopsy (SLNB), or sentinel node biopsy (SNB). This technique consists in injecting a radioactive tracer or blue dye into the breast to surgically detect the first lymph node(s) likely to harbour metastases if the cancer has spread. The anatomical pathology examination of these sentinel nodes is a good indicator of the status of the other axillary lymph nodes. Theoretically, if the sentinel nodes are free of metastases, so are the other axillary lymph nodes. Sentinel node biopsy therefore avoids axillary dissection in patients whose sentinel nodes are free of metastases.

Although several technical protocols for performing sentinel node biopsy exist, there are no standards defining best practices. The Comité de l'évolution des pratiques en oncologie (CEPO) therefore asked AETMIS to conduct a systematic review of the validity of current evidence on the technical aspects of sentinel node biopsy in breast cancer treatment with a view to providing appropriate guidance on this medical procedure in Québec.

### Research Method

This report is a systematic literature review of the feasibility and diagnostic accuracy of sentinel node biopsy. The two main study parameters are sentinel node identification rate and risk of false negatives (1 - negative predictive value). For analysis of the false-negative risk, all the study patients had to have undergone axillary dissection. The technical aspects of sentinel lymph node biopsy assessed in this report include type of tracer (radioisotope or blue dye, or both); type of radioactive colloid (sulphur colloid, albumin colloid, or other); type of dye (patent blue, isosulfan blue, methylene blue, or other); tracer injection site (deep or superficial injection, and variants); time from injection to surgery; use of preoperative lymphoscintigraphy or not; histological examination method (with or without immunohistochemistry); and intraoperative examination. This report also addresses the role of the learning curve for this technique.

### Results

This assessment pooled the results of 3 systematic reviews and 32 primary studies. The results of a meta-analysis of 183 studies showed that the sentinel node identification rate was higher with the isotope technique (94.3%) than with the blue dye technique (87.5%). Similarly, two meta-analyses, a randomized controlled trial and three new prospective multicentre cohort studies demonstrated that the combined technique (identification rate ranging from 90% to 100%) was superior to the blue dye technique. The combined technique offered a modest benefit over the isotope technique, but the difference (1.6%, according to one meta-analysis) may not be clinically significant. This variable has not been subjected to a randomized controlled trial. Furthermore, on a very large sample, the risk of false-negative findings may be higher with the blue dye technique than with the combined technique.

According to the results of a meta-analysis, the type of radioactive colloid and dye does not seem to significantly influence either the sentinel node identification rate or the risk of false negatives.

The sentinel node identification rate with a dye is routinely higher when the injection is superficial rather than intraparenchymal; a meta-analysis of 142 studies found a significant difference between peritumoural injections (93.2%) and periareolar or subareolar injections (96.5%). However, this significant difference was not reported in two randomized controlled trials (RCTs) published after the meta-analysis. The injection site may not affect the risk of false negatives.

Superficial periareolar or subareolar radioisotope injection yields better identification rates than deep peritumoural injection (4.4% difference). This result, derived from a meta-analysis of 141 studies, was not confirmed in two randomized controlled trials with smaller sample sizes (500 and fewer patients) but was confirmed in a large cohort study (more than 4000 patients). The results of the same meta-analysis indicate that superficial intradermal or subdermal injection above the tumour site yields a higher identification rate than peritumoural injection (2.4% difference), a result confirmed in a randomized controlled trial and a prospective cohort study. However, the injection site may not affect the risk of false negatives.

The timing of radioisotope injections (the day before or the day of the surgery) does not affect the sentinel node identification rate (95.1% vs 94.3%) when the administered dose is adjusted accordingly. These results were obtained from a meta-analysis of 112 studies; four additional studies, including a non-randomized controlled trial, did not report a significant difference. However, the risk of false negatives seems slightly higher if the injection is administered the day before surgery (5.7% vs 3.5%).

Preoperative lymphoscintigraphy is an additional examination designed to detect axillary sentinel lymph nodes after radiotracer injection. According to a small non-randomized controlled trial and a prospective multicentre cohort study, preoperative lymphoscintigraphy increased neither the sentinel node identification rate nor the sensitivity of sentinel node biopsy for detecting axillary lymphatic involvement. In the majority of cases

(68–99%) in which no sentinel lymph node was detected by lymphoscintigraphy, a sentinel lymph node was nonetheless identified during surgery.

Regarding the histopathological analysis of sentinel node specimens, the use of immunohistochemistry combined with standard histological analysis (hematoxylin-eosin staining) provided highly variable results: the conversion rate of negative results into positive results through the addition of an immunohistochemistry examination ranged from 0% to 52% in 31 studies that analyzed 1750 negative findings on definitive histological examination. The conversion rate indicates the proportion of patients who receive negative results on routine histological staining but positive results for metastasis detected by immunohistochemistry. Moreover, immunohistochemistry seems neither to increase the sentinel node identification rate nor to reduce the false-negative risk.

Intraoperative histological examination is performed during surgery to guide the decision whether or not to proceed with axillary dissection. Two intraoperative techniques are used: frozen section and touch imprint cytology. According to a meta-analysis of 31 studies, the sensitivity of intraoperative examination was lower (average of 63%) than that of definitive histological analysis for detecting the presence of sentinel lymph node metastasis. The sensitivity of intraoperative examinations was higher for detecting macrometastases (average of 81%) than micrometastases (average of 22%). The proportion of false negatives associated with micrometastases on intraoperative examination was 82%. The sensitivity of frozen-section examination is probably higher than that of touch imprint cytology (76% vs 62%). For both techniques, the specificity of the intraoperative examination was very high (99%), which means a low risk of false positives.

Surgeon and team experience influence identification rates. Appropriate surgeon performance is achieved with 50 or fewer biopsies, and generally with fewer than 20 biopsies. A high sentinel node identification rate, predictive of a low risk of false negatives and a high sensitivity, could serve as a performance indicator.

## Conclusions

Sentinel node biopsy is a proven technique in terms of feasibility and diagnostic accuracy. In experienced hands, it generally yields high identification rates and has a low risk of false negatives (1 - negative predictive value). Certain technical aspects nevertheless influence these performance measures. For maximum success rates, the following technical protocols are suggested:

- The use of radioisotope alone is better than the use of blue dye alone. Combining the two tracers achieves the best identification rates and the lowest risk of false-negative findings. The difference between the combined technique and the isotope technique alone is not statistically or clinically significant, so the potential risk of allergic reaction must be considered in selecting the technique to adopt.
  - The different types of dyes and radioactive colloids do not substantially modify the results of sentinel node biopsy.
  - Superficial injection of the tracer (periareolar, subareolar, supratumoural administered intradermally or subcutaneously) offers better success rates in identifying sentinel nodes than intraparenchymal injection. However, the injection site does not affect the risk of false negatives.
  - The time from radioisotope injection to surgery is not meaningful if the dose is increased for injection administered the day before the procedure. However, the risk of false negatives may be slightly higher for injection given the day before surgery.
- Preoperative lymphoscintigraphy appears not to improve either sentinel node identification rates or the sensitivity of sentinel node biopsy for detecting axillary lymphatic invasion.
  - Immunohistochemistry combined with standard histological examination (hematoxylin-eosin staining) achieves highly variable results and does not seem to reduce the risk of false negatives in sentinel node biopsy. Its use is optional at this time. The prognostic value of micrometastases detected solely through immunohistochemistry is currently under investigation.
  - Despite low sensitivity for detecting micrometastases, intraoperative examination of sentinel nodes by imprint cytology or frozen section offers the possibility of immediate axillary dissection in the event of positive intraoperative findings.

Surgeon experience affects sentinel node identification rates but has a lesser impact on the risk of false negatives. The learning curve seems short: high performance levels may be achieved with as few as 20 biopsies under the supervision of a qualified surgeon. Sentinel node identification rate could subsequently serve as a performance indicator.