

Guideline Title:	Sentinel Node Biopsy in Breast Cancer	Date:	(O): (R):	Nov 30, 2011
Tumor Group:	Breast Disease Site Group	Page:	( )	1 of 9
Issuing Authority:	Dr. Rod Martin Clinical Chief, Surgical Program	Date Signed: February 15, 2013		
Adapted From	The Cancer Care Ontario's "Sentinel Lymph Node Biopsy in Early- Stage Breast Cancer: Guideline Recommendations", July 2009 (52).			

#### Introduction:

The accurate assessment of the axillary lymph node status is an excellent prognostic indicator of the risk of developing distant metastases in the patient diagnosed with breast cancer. It is also crucial in determining the adjuvant systemic and locoregional treatments required. For many years, the 'gold standard' had been axillary lymph node dissection (ALND), which provides excellent regional control but is associated with potential long-term morbidities including impaired range of motion, lymphedema, pain, nerve injury, and weakness (1). It may also be an unnecessary procedure for 70-80% of node-negative breast cancer patients.

Sentinel lymph node biopsy (SLNB) has emerged as an accurate, minimally invasive procedure to assess axillary nodal status in patients with operable breast cancer. A sentinel node (SN) is any node or nodes receiving lymphatic drainage from a primary tumor site, and studies have shown that the presence of metastases there is indicative of the status of the rest of the axillary nodes (2). The sentinel node biopsy procedure requires the combined the expertise of three fields of medicine – surgery, radiology and pathology. The procedure involves the use of blue dye and/or radioactive isotopes injected locally around the cancer to locate the SN(s). These nodes are then removed surgically and examined by the pathologist to determine if there are any cancer cells present. If the SN is deemed to be positive for cancer or unable to be identified, the surgeon will proceed with performing an ALND.

#### **Questions:**

- 1. Does the evidence support the use of SLNB in the clinically lymph node negative patient versus the use of ALND?
- 2. What are the patient selection criteria for the use of SLNB in breast cancer?
- 3. What is the optimal technique for the use of SLNB in the treatment of breast cancer?

## **Target Population:**

The recommendations are aimed toward patients who have been diagnosed with cancer of the breast and meet the selection criteria for SLNB.

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#### **Supporting Evidence and Recommendations:**

• <u>SLNB versus ALND</u> - In the Cancer Care Ontario (CCO) SLNB 2008 guideline, the evidence review revealed four randomized control trials (RCTs) comparing SLNB to ALND, which reported high SN detection rates from 95.1% to 97.2% and accuracy rates from 94.4% to 97.6% (52). The false-negative rates were low and node-positive rates were similar between ALND and SLNB-alone arms (3-6, 52). The Sentinella-GIVOM non-inferiority trial also revealed only one axillary recurrence in 345 SN-negative patients at 55.6 months of follow-up, and similar disease-free and overall survival rates between the two arms (7). Since the CCO guideline was published, our literature search revealed 3 more RCTs, a meta-analysis, and a 10 year follow-up study of a RCT, which all confirm the equivalency of SLNB to the ALND in early stage breast cancer (8-12).

**Recommendation:** All patients with early stage breast cancer, without clinically or pathologically positive lymph nodes, should have a SLNB to stage the axilla.

• <u>Eligibility Criteria\*</u> - The Sentinel Lymph Node working group agrees that the best evidence to date supports the use of SLNB in patients with early breast cancer, who have T1 or T2 unifocal tumors that are less than or equal to 3 cms in diameter and clinically negative nodes.

Circumstances where SLNB would not be recommended:

- inflammatory or T4 breast cancer
- prior axillary surgery (unless minimal).

The clinical circumstances for patients with breast cancer where the evidence is *inconclusive* or *inadequate* are those with:

- T3 or T4 (tumors larger than 3 cm in diameter) tumors
- internal mammary lymph nodes
- multifocal tumors
- before neoadjuvant therapy
- DCIS treated by lumpectomy
- pregnant or breastfeeding women
- known allergies to blue dye
- previously treated breast cancer or non-oncologic axillary surgery on the affected breast (52).

**Recommendation:** Patients with early stage breast cancer, who have T1 or T2 unifocal tumors, that are less than or equal to 3 cms in diameter, and have clinically negative lymph nodes should be eligible for SLNB.

• <u>Technique</u> - The identification of the SN(s) is carried out with the use of lymphoscintigraphy, which is defined as the scintillation scanning of the lymphatics or lymph nodes following intralymphatic or subcutaneous injection of a radionuclide. The breast is injected intradermally with a combination of a small amount of filtered technetium-99m sulfur colloid and local anaesthetic, a gamma camera is then used to capture an image of the lymphoscintigraphic

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\*Adapted from the CCO guideline "sentinel node biopsy in early-stage breast cancer" (52). pattern of the breast. The 'mapping' or marking of the location of the sentinel node(s) on the patients' skin, to aid in their removal, can be performed by the nuclear medicine physician or later by the surgeon intraoperatively. Blue dye is often injected into the breast intraoperatively by the surgeon has an additional mapping agent and carries a very small risk of causing an allergic reaction, with anaphylaxis occurring approximately once every 3000 cases. The blue dye is also especially helpful in identifying SN(s) that are diffusely metastatic which would interfere with the SN's capacity to retain the radiocolloid (13).

Breast injection of the radioisotope can be performed up to 24 hours prior to the SNB procedure, but is usually injected approximately 30 to 60 minutes preoperatively in the nuclear medicine department at Eastern Health. The superficial injection technique used allows for rapid flow of the radiotracer to the breast lymphatics enabling the completion of lymphoscintigraphy in a timely fashion (14-16). Though rare, if the SN(s) are not visible with the first injection, a second injection of radiotracer can be administered without compromising accuracy (17,18).

The literature suggests that where possible lymphatic mapping with pre-operative lymphoscintigraphy and a combination of radioisotope and blue dye should be used to locate the SN(s), as this may be associated with a higher rate of detection (19,20,49). Accurate SN detection can also be provided by using either blue dye or radioisotope alone (such as unfiltered/filtered 99mTc sulphur colloid), when the combination technique is unsuitable or unavailable (3,12,21).

**Recommendation:** Preoperative lymphoscintigraphy is the preferred standard of care where available. The combination use of radioisotope and blue dye is preferred though using either alone is acceptable.

There has been considerable debate on where best to inject the radiotracer colloid and/or dye to achieve the maximum visibility of the SN.

**Recommendation:** The combination approach of intradermal, periareolar of colloid injection is preferred by the nuclear medicine program within Eastern Health (22-24). Frequently, gentle massage is used over the injection site to help facilitate the clearance of the radiocolloid (25). The blue dye injection is given in the upper outer quadrant of the areola. If the patient has had a previous surgery (ex. previous breast biopsy) in this area, the injection is always given above the scar to ensure the scar tissue does not interfere with the dispersion of the isotope/dye to the SN(s). The surgeon then uses a hand held detection probe to identify the location of the radioactive SN(s).

Recently, there has been a renewed interest in mapping the internal mammary lymph nodes but the Sentinel Lymph Node working group agreed that there is not enough quality evidence to pursue this currently.

• <u>Pathology</u> - During the intraoperative SLNB procedure, the pathologist has to be at the ready and available to receive the SN specimens from the operating room. To allow timely and efficient processing of the specimens, a completed pathology requisition from the surgeon should accompany them. The surgeon should indicate which node is believed to be sentinel. The pathologist will process the SN(s) via frozen section examination as per Eastern Health's

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pathology protocol, and communicate the result to the surgeon as promptly as possible (26,27,44).

# **Challenging Clinical Situations**

• <u>ALND when SN is Positive</u> - the standard surgical treatment for a positive SN (including micrometastases), or when the SN(s) are unable to be identified, is a Level 1 or 2 ALND (7,8,11,12,28-30). However, available evidence suggests that more than half of the SN positive patients have axillary lymph node metastases limited only to the SN. Therefore, there may be low-risk subsets (ie. isolated tumor cells, micrometastases) that may not warrant an ALND (31-35).

The working group feels that such a case would require a balanced discussion between the surgeon and the patient regarding the risks of further surgery and any potential for improved outcome with more information obtained from an axillary clearance. The TNM classifies isolated tumor cells, located in the regional lymph nodes, which are less than 0.2mm in its greatest dimension has pN0. Micrometastases, on the other hand, are tiny metastases that are larger than 0.2mm but smaller than 2.0mm in its greatest dimension and are classified has pN1m1 (49).

• <u>Intraoperative Assessment of SN(s)</u> - may offer patients a one-step operation. Intraoperative SN diagnosis of metastasis would allow the patient and surgeon the opportunity to complete the recommended lymph node dissection in a single operative setting. The extra cost associated with the intraoperative assessment would be balanced out by the savings related to the cost of a second operation, a second exposure to anaesthesia, and a potentially more challenging operative field (36).

# The working group feels that the intraoperative assessment of SN is preferable but not always possible or practical, operating within the framework of available resources within the province.

• <u>Ductal Carcinoma In situ (DCIS)</u> - recent evidence suggests that around 20% of patients initially diagnosed with DCIS on a needle core biopsy will be found to have invasive breast cancer at the time of definitive breast surgery (37-40). This indicates that there are subgroups of patients, diagnosed with DCIS, who are at highest risk of having an invasive component. An analysis of the evidence suggests the rate of upstaging DCIS to invasive disease is related to the size of the mass, and that a mass large enough to be clinically palpated and/or mammographically detected was an independent predictor of invasive disease (39). The presence of extensive DCIS in the breast requiring mastectomy also has been found to increase the risk of an invasive component (41).

The consensus of the working group was that SNB should be performed on those select patients with a breast mass detected by clinical exam or by mammography, and those with extensive lesions requiring mastectomy.

• <u>Multiple Sentinel Nodes</u> - the presence of more than one SN is usually noted in the majority of patients and identification of these multiple SN(s) is important to reduce the false negative rate (5,42). Evidence suggests however that the surgeon is able to identify 99% or more of

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node-positive patients without incurring further morbidity if he forgoes sampling after 4 nodes (43).

The consensus of the working group was that removing more than 4 nodes will lead to minimal improvement in accuracy while potentially adding to the morbidity.

• <u>Surgical Training</u> – clinical trials required the performance of approximately 20 sentinel node biopsy procedures followed by an axillary lymph node dissection by the surgeon for validation (6,8,29). The American Society of Breast Surgeons suggests that the learning curve for SLNB can be much shorter for surgeons with a well-standardized technique, since most failed results occur within the first few cases (45).

Since no standard exists, the working group believes that the surgical privilege of performing SLNB should be in accordance with each health care region's policies and procedures. The working group recommends that being mentored by an experienced colleague would be optimal to minimize false-negative results.

• <u>Recent Advancements</u> - the working group discussed the use of preoperative axillary ultrasound and biopsy of all clinically node-negative patients, and the use of reoperative or 'remapping' the SLNB for those who develop ipsilateral breast recurrence or second primary cancer.

In both cases, the group felt that there was not enough evidence to qualify either as standard of care at this present time.

#### **Recommendation:**

Patients, who have been diagnosed with cancer of the breast, should be eligible for sentinel lymph node biopsy when they meet the selection criteria for its use.

## Search Strategy:

Literature searches were conducted in Pubmed and the Cochrane Library and using keywords "sentinel node biopsy" AND "breast" AND "neoplasms" and also "guidelines". Guideline searches were also carried out on the websites of North American's most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 2005 (unless the selection was a landmark study) up to November 2011. The inclusion/exclusion process consisted of selecting guidelines from reputable international cancer organizations, with preference given to those from Canadian sources where possible. Ten source guidelines were identified and conformed to our search criteria, from which five were selected due to currency, quality of content and/or were Canadian in origin (45-54).

The five identified source guidelines (50-54) were put through the ADAPTE process (55) including an AGREE II assessment (56), and the Cancer Care Ontario "sentinel lymph node biopsy in early-stage breast cancer" guideline was chosen to be adapted for use in our guideline (52). The CCO guideline was selected as the optimal choice due to its applicability, quality and currency of content.

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No competing or conflicts of interest were declared.

#### **Disclaimer:**

These guidelines are a statement of consensus of the Breast Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

#### **Contact Information:**

For more information on this guideline, please contact Dr. Christopher Cox MD FRCSC, St. John's, NL; Telephone 709-237-7022. For access to any of our guidelines, please visit our Cancer Care Program website at <u>www.easternhealth.ca</u>

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