



BC Surgical Oncology Network

Provincial Guidelines For Lymphatic Mapping And Sentinel Node Biopsy For Breast Cancer

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ABSTRACT

Objective

To develop a consistent approach for radioguided identification, surgical retrieval and pathologic assessment of sentinel lymph node(s) (SLN) biopsies in women with early breast cancer in British Columbia.

Target Audience

Surgeons, radiologists and pathologists involved in the assessment and treatment of invasive breast cancer in British Columbia.

Outcomes

Sentinel node identification rate, false negative rate, morbidity of axillary surgery.

Evidence

Recent literature on Sentinel lymph node biopsy, review of the NSABP Protocol B-32 and review of current sentinel lymph node practice in BC were used to synthesize this report.

Benefits and Harms

Improved sentinel node detection rate, reduced false negative rate, reduced surgical morbidity in axillary dissection.

Recommendations

- Centres that elect to perform sentinel lymph node biopsy for breast cancer patients require a multidisciplinary approach, coordinating the efforts of radiology, surgery and pathology divisions.
- Appropriate training and skills development for participants from each division is mandatory.
- Indications include women with T1 and T2 breast cancers.
- Contraindications include patients with advanced breast cancer conditions, multifocal cancers, previous disruptive breast procedures (surgery, radiation), palpable axillary nodes, adverse reactions to vital dyes and inability for the patient to give consent.
- Sterile technique should be used for invasive breast imaging and surgical removal of the sentinel lymph node.
- A combined technique for sentinel node imaging using radiotracer (37 Mbq of 99mTc Sulphur Colloid) and 5ml of 1% Isosulfan blue dye maximizes detection rates.
- Radiotracer and isosulfan injections should be given peritumourally within 1 cm of the cancer or biopsy cavity.
- An option of using a subdermal injection of contrast has been found to increase detection of sentinel nodes.
- Preoperative sentinel node imaging in the nuclear medicine department has been found to assist surgeons to successfully identify sentinel node(s) intraoperatively.
- All patients should undergo level 1 and level 2 axillary dissection if the sentinel node(s) are reported positive for malignancy, if the surgeon is unable to identify a sentinel node or as part of the Surgeon's training and validation process.
- Standardized documentation and data collection is necessary from all departments (radiology, surgery, pathology) for the determination of institutional and surgeon specific case volume, sentinel node identification rate and false negative rate.

Validation

This is the original guideline. The Guideline was endorsed by Breast Cancer Tumour Group of the British Columbia Cancer Agency November 21, 2003.

Sponsor

Surgical Oncology Network of the BC Cancer Agency

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BACKGROUND

Axillary node metastasis is the most powerful prognostic factor available for patients with primary breast cancer (level IV & V evidence)¹. Accurate assessment of the axillary lymph node status provides important prognostic information and guides the selection of women for adjuvant therapy. Axillary lymph node dissection provides excellent regional control and has been the standard of care for women with invasive breast cancer (level I evidence)² (level III evidence)³⁻⁵. This procedure however, is associated with potential morbidity, including post-operative pain, seroma, painful neuroma, neuropathies, and lymphedema (level III evidence)^{6,7}.

Screening mammography continues to increase the proportion of women diagnosed with node-negative breast cancer (level I evidence)³. Lymphatic mapping combined with sentinel node biopsy, has been compared to sentinel node biopsy plus total axillary node dissection in 516 women with primary breast cancers ≤ 2 cm and found to be a safe and accurate method of screening the axillary nodes. The overall accuracy of the sentinel node status was 96.9%, the sensitivity was 91.2% and the specificity was 100%. There was less pain and better arm mobility in the patients who underwent sentinel-node biopsy only compared to those who had sentinel node biopsy plus axillary node dissection. In this study there were no cases of overt axillary metastases during follow-up in the 167 patients who did not undergo axillary node dissection (level II evidence)⁵.

A successful sentinel node biopsy program requires a multidisciplinary collaborative effort involving the surgeons, nuclear medicine physicians, and pathologists (level III evidence)¹⁰. The sentinel node hypothesis is that the pathologic status of the sentinel node, the first node in the regional lymphatic basin that drains the primary tumour, accurately reflects the histologic status of the entire regional lymph node basin (level III evidence)¹¹⁻¹⁴ (level IV & V evidence)¹⁵⁻²³. Sentinel node biopsy involves much less surgery than conventional axillary dissection and may permit rapid return to normal activity and reduce long-term sequelae (level IV & V evidence)^{24,25}. This would reduce patient morbidity and improve quality of life.

PURPOSE

To develop provincial guidelines based on evidence-based clinical practice that enables a standardized approach to lymphatic mapping and sentinel node biopsy for patients with breast cancer. These guidelines will be presented to the provincial Breast Cancer Tumour Group of the British Columbia Cancer Agency for review and endorsement. It is the expectation that these guidelines will harmonize the sentinel node practice observed in British Columbia (level III evidence)²⁶ and lead to improved consistency and quality of care for breast cancer patients.

PATIENT SELECTION CRITERIA

Indications

- T1/T2 palpable or non-palpable invasive adenocarcinoma with clinically negative axillary lymph nodes.

Contraindications

A- Advanced breast cancer conditions

- T3/T4 lesions
- Locally advanced or inflammatory breast cancer.
- Multicentric breast cancer.
- Clinically positive (palpable) axillary node(s).
- Clinically positive supraclavicular lymph node(s).
- Metastatic breast cancer.

B- Relative Contraindications- Due to the nature of previous treatments that have rendered the breast “disrupted” the reliability of SLNB in such circumstances as a stand-alone procedure may be placed into question.

- Previous surgical resection for breast malignancy.
- Previous removal of any ipsilateral axillary lymph node(s).
- Previous breast irradiation.
- Pre-operative chemotherapy.
- Breast implants.
- Previous reduction mammoplasty.

C- Other contraindications-

- Adverse or allergic reactions to Blue dye (isosulfan blue) or 99mTc sulphur colloid radionuclide
- Patients unable to give informed consent for SLN biopsy

D- Other Considerations-

- Pregnant patient (Potential effects to the unborn fetus) (level III evidence)^{27,28}
- Breast feeding (Potential effects on the newborn)

GENERAL PRINCIPLES

- 1) Sterile technique should be employed for all invasive procedures of the breast and axilla in accordance to local hospital practice and guidelines.
- 2) A combined use of blue dye and radio-pharmaceutical (99mTc sulphur colloid) dye has been found to increase sentinel node detection rate (level IV & V evidence)¹⁵.
- 3) Sentinel nodes should be submitted separately and clearly marked for pathologic assessment.
- 4) Sentinel node biopsy is to be recognized as a diagnostic study and not a therapeutic procedure.
- 5) Failure to identify sentinel node(s) at the time of surgery should lead to level 1 and 2 axillary node dissection.

RADIOLOGIC PROCEDURES

Nuclear Medicine

Currently no standardized technique for sentinel

node localization exists (see “Controversies in Breast Lymphoscintigraphy” below).

- Patient registration in the nuclear medicine department 60 min to 16 hours prior to the planned surgical procedure.
- Optimal time for breast injection of 99mTc sulphur colloid is 3 hr. before surgery with a minimum preoperative time interval of 1 hr. pre-op. Injections can be administered as the last case of the day in nuclear medicine with surgery taking place as the first case the following morning.

Radio-pharmaceutical

- Unfiltered 99mTc sulphur colloid (optional- filtered)

Technique

- 1) Injectate- A total volume of 8 mls (level III evidence)²⁸ containing one mCi (37Mbpq) of 99mTc sulphur colloid, 2-4 mls of 1% lidocaine and sterile saline.
- 2) Using a 25 or 27 gauge needle, equal boluses of radio-pharmaceutical mixture are injected into six sites around the tumour, four circumferentially and one each above and below the tumour.
- 3) Radiologist injects peritumorally into normal breast tissue within 1 cm of the primary tumour or margins of (but not into) the biopsy cavity.
- 4) Injection will be guided by palpation, ultrasound or mammography depending on the clinical situation.
- 5) Patients with non-palpable tumours will have wire localization inserted by mammogram or ultrasound and the radiocolloid will be delivered using a single injection through the needle.
- 6) Patient is instructed to massage the injection site for 5 minutes.
- 7) The skin area is washed afterward injection to remove any 99mTc sulphur colloid contamination on skin.
- 8) Pre-operative lymphoscintigram (prior to transfer to the surgical suite) has been determined to improve sentinel node identification rate (level III evidence)²⁹.
- 9) Documentation: Injection date and time, amount of radio-pharmaceutical used, difficulties or complications.

Controversies in Breast Lymphoscintigraphy

In trying to develop a Breast Cancer consensus position and Provincial guideline for lymphatic mapping and sentinel node biopsy, it is appreciated that there are different lymphoscintigraphic methodologies. Such controversies can be listed under the following four categories (level IV & V evidence)³⁰: 1- Size of radioactive particles (level II evidence)³¹ 2- Volume of radioactive tracer used (level III evidence)²⁸ (level IV & V evidence)²⁰ 3- Location of the injection of radiotracer (intradermal (level I evidence)³² (level III evidence)³³, intratumoural (level III evidence)³⁴, peritumoural (level III evidence)²⁸ (level IV & V evidence)²¹, subareolar (level III evidence)³⁵, subdermal (level IV & V evidence)²³, subperiosteal (level III evidence)³⁶ 4- Assessment of the internal mammary

nodes. This guideline will be modified accordingly when further clarity within these categories is defined.

There is growing recognition that intradermal injection of radiotracer can yield superior axillary sentinel node identification rates when compared to the peritumoural technique. Intradermal injection is simpler and both intradermal and peritumoural techniques show excellent concordance when compared to isosulfan blue dye studies (level I evidence)³² (level III evidence)³³. Intradermal injection of 99mTc sulphur colloid alone has the significant disadvantage in that it does not image potential SLN within the internal mammary chain (level I evidence)³¹ (level III evidence)³³ (level IV & V evidence)²³. In March 2001, the NSABP-B32 protocol was modified to include subdermal radiocolloid injection with peritumoural injection of radiocolloid and blue dye (level IV & V evidence)³⁷.

Optional- Intradermal injection of radiotracer

- The apparent improvement in axillary sentinel node identification with an intradermal injection of radiocolloid combined with the evidence that peritumoural injection is necessary to image all potential sentinel nodes (including the internal mammary), has lead some to advocate that a combined approach using additional intradermal injection be administered at the time of the peritumoural injection.
- A separate syringe containing 0.2mCi of filtered 99mTc sulphur colloid diluted in 0.5mL sterile saline is used. Patients with prior core needle or fine needle aspiration biopsies will have the entire 0.5ml injected intradermally into the skin immediately above the tumour site in the breast, regardless of whether the lesion is palpable or non-palpable. Patients with prior excisional biopsies will have the 0.5 ml injected intradermally on the side of the incision that directly faces the axilla, within 0.5 cm of the incision near the midpoint of the incision.

SURGERY

General Comments

- Surgeons will have undergone appropriate training in the technical aspects of sentinel node biopsy.
- Surgeons should keep an up to date record of:
 - 1) Number of sentinel node procedures performed
 - 2) Sentinel node identification rate
 - 3) False negative rate [defined as = FN / (FN + TP) where FN is false negative and TP is true positive].
- Prior to offering sentinel node biopsy as a stand-alone procedure, the attending surgeon should have a false negative rate of less than or equal to 5% in their last 20 consecutive cases.
- All patients with a positive sentinel node (axillary or internal mammary) should undergo a Level 1 and 2 axillary node dissection. This includes patients in whom the sentinel node may have been interpreted as normal intraoperatively but was later determined on H&E or immunohistochemistry to contain cancer.
- All patients in whom the sentinel node was not identified

should undergo a Level 1 and 2 axillary node dissection (the proviso being that the axillary node dissection will alter therapy, i.e. age)

Operative Technique

- Within 60 minutes to 16 hours following injection of ^{99m}Tc sulphur colloid, the patient will be taken to the OR. The breast and axilla will be prepped and draped in sterile fashion. It is recommended that a sterile camera drape be placed over the probe, and if an open end is present, to cover it with a sterile glove.

1- Mapping out the zone of diffusion

- The radiotracer will diffuse into breast parenchyma around the site of injection; this is the zone of diffusion. The background “noise” within this zone will obscure detection of a radiolabelled node. The borders of this zone thus require mapping. To do this, a dot is made with a sterile marker at the location where the audio signal peaks out at a given setting. These marks are made circumferentially around the injection site, and a resultant circle is created with a marker by connecting the dots. Hot spots can now be sought beyond the diffusion zone.

2- Initial Survey

- A hotspot is defined as a discrete area of increased radioactivity, which is higher than the background count between the hotspot and injection site (diffusion zone).
- The surgeon will carefully evaluate the patient for discrete hotspots in the regions of potential lymph node-bearing tissues by working from the boundaries of the zone of diffusion.
- The areas examined will include the axilla, supraclavicular fossa, cervical, internal mammary, upper abdomen and intramammary locations.
- The proper technique is to start at the margins of the diffusion zone and scan straight out in a radial fashion. The audio feedback of counts should gradually decrease the greater the distance one gets from the injection site. If a sentinel node is present, it will signal as a sharp increase in the number of counts heard over the small area immediately above the node.
- All possible hot spots should be marked with a sterile marker, and the completion of the primary survey should continue until the full 360-degree area around the injection site is scanned. If other audio feedback level settings are available, the same procedure is performed beginning at the edge of each settings zone of diffusion.

3- Pre-incision hotspot counts

- A pre-incision 10-second count helps to identify the position of the hotspot(s) and assists in planning where the incision is to be made.
- A 10-second count should be taken directly over the area of maximal audio feedback and recorded.

4- Difficulty finding a hotspot

- If one has difficulty locating a hotspot prior to making an

incision, this can be due to one or more of three possible problems.

- 1) Overlap of the injection diffusion zone over the regional nodal basin. This is more pronounced in upper outer quadrant tumours for the axillary nodes and in upper inner quadrant lesions for the internal mammary nodes. The solution to this problem is to manually retract the breast away from the axilla, to angle the probe away from the injection site, to apply gentle pressure on the skin with the probe to “push away” subcutaneous tissue.
 - 2) Probe threshold too high. The threshold levels on the probe can be dialled down, which will increase the sensitivity level. As the threshold is decreased, the background noise will increase, so one must balance this out to get the best setting for hotspot detection.
 - 3) Inadequate radio-colloid in the sentinel lymph nodes. This may be a problem with fat-replaced breasts, which have relatively fewer lymph node channels than dense fibro-glandular breasts.
- If a hot spot is not identified using the techniques described above, the surgeon should try to enhance lymph drainage to the sentinel node. This can be accomplished by increasing the interstitial pressure by injecting 7-10cc sterile saline into each of the same locations injected with radio-colloid (40 cc total volume). Gentle massaging of the area may also enhance lymph flow. The surgeon will allow 10 minutes for migration of the tracer to the sentinel lymph nodes. This procedure has been associated with a 70% detection rate of the sentinel node when one was not identified in the initial survey (level IV & V evidence)²⁰.
 - If a hotspot is still not identified after the 40 ml saline bolus, then the surgeon will inject the blue dye as described below. Following this, the surgeon will make an incision in the lower axilla and will try to locate the sentinel node by 1) placing a gamma detector directly into the axillary tissue and 2) blunt dissection of the axillary tissue in order to locate blue-stained lymphatic ducts that lead to a sentinel node.
- #### *5- Injection of Blue Dye*
- Blue dye injection should be performed in the operating room under sterile conditions.
 - All patients will be injected with 5cc of Isosulfan Blue (lymphazurin), after completion of detailed lymphatic mapping of the radiotracer. (The risk of anaphylaxis, “blue hives” or other significant allergic reaction is 2%)
 - If no “hot” sentinel node is detected during the initial survey with the gamma probe, then the blue dye should be injected after a 40 ml saline bolus injection as described above.
 - The dye should be injected into the parenchyma between the sites where the ^{99m}Tc sulphur colloid was injected. This helps ensure that there are no skipped areas encountered.
 - At least 5 minutes should pass between blue dye injection

and sentinel node harvest.

- The breast should be gently massaged at the injection site to enhance lymphatic flow.

6-Axillary Incision

- A 2-3 cm incision and dissection in the axilla should be guided by the gamma probe. Typically the incision is often situated close to the inferior border of the axillary hair line.
- If a hotspot is not found or if the only hotspot identified is outside the axilla, an incision in Level I of the axilla, which could be extended to a full axillary dissection incision, should be made.

7- Surgical removal of the radiolabelled nodes

- Localization of the sentinel node(s) within the nodal basin requires dissection using a combined approach of focusing the gamma probe on the highest audible count, observing for blue stained ducts or nodes and palpating for abnormally hard and enlarged lymph nodes.
- Sentinel nodes are defined as lymph nodes that are:
 - 1-hot
 - 2-blue
 - 3-both (hot and blue)
 - 4-palpably hard
 - 5-non-stained node but found at the termination of a blue-stained lymph duct.
- Blue ducts should be followed in both directions to verify the node to be removed.
- When the hot lymph node is encountered, care should be taken to completely excise it. Clips should be used when detaching the node from the lymphatic channels to prevent spillage of blue dye and radioactive contrast.
- A 10 second ex-vivo count of the resected node is performed by placing the node on the tip of the probe. To ensure an accurate sentinel node count, the probe is positioned extraneous from the surgical field to avoid the potential interference from counts derived from the diffusion zone.
- After removal of a radiolabelled node, the probe should be re-inserted into the wound. Any additional nodes identified with counts $\geq 10\%$ of the hottest sentinel node, should also be excised. After all radiolabelled nodes are removed; a 10-second post excision bed count is taken to document completion of the procedure.
- Sentinel node dissection is complete when there are no blue stained, or hard palpable nodes present, and the post excision bed count is less than 10% of the hottest sentinel node removed.
- Each sentinel node is submitted denoting rank order, position, and count score.

8- Completion lymphadenectomy

- Level 1 and 2 axillary node dissection is indicated for the following:
 - 1) Positive sentinel nodes as determined by H&E on permanent pathology.
 - 2) Positive sentinel nodes as determined by H&E touch prep or frozen section. Depending on institutional

feasibility, the sentinel nodes may be evaluated intraoperatively in this manner for metastases to determine whether to proceed with immediate completion axillary lymphadenectomy. Ideally axillary node dissection will occur immediately following positive verification of disease within the sentinel node.

- 3) Positive sentinel nodes as determined by immunoperoxidase staining.
- 4) Grossly positive, clinically palpable nodes.
- 5) When the sentinel node procedure failed to identify a sentinel node.
- 6) As part of the Surgeon's training and validation process.

- The incision for the sentinel node removal in the axilla should be placed so that it will function as a portion of the axillary dissection incision.

9- Removal of the internal mammary lymph nodes

- Five to ten percent of patients are expected to have lymphatic drainage that can be traced to the internal mammary nodes. These nodes are usually located lateral to the sternal border in the 2nd and 3rd interspace. If an internal mammary hotspot is found, the labelled nodes should be removed with a 2-3cm incision over the hotspot. The incision is extended down through the pectoralis and intercostal muscle fibers, splitting them along the course of their fibers. The node(s) are usually small and surrounded by fat and usually located between, rather than under the ribs. Care should be taken to avoid vessel injury or violating the underlying pleura. If the pleura is entered then the pleural space should be evacuated of extraneous air on closure using a red rubber catheter and generous positive pressure insufflation to minimize residual pneumothorax.
- Ex vivo counts of the excised nodes and post-excision bed counts should be performed as previously described.

10- Resection of sentinel nodes other than axillary or internal mammary nodes

- Sentinel nodes can be removed from below the clavicle, very low axilla, and upper abdominal wall. Such sentinel nodes should be removed with the smallest possible incision.
- It is acceptable to leave sentinel nodes unresected if they are located in a place where removal would cause significant morbidity (*i.e.* intra-abdominal or intra-thoracic).

11- Sentinel node labelling

- All sentinel node(s) are submitted individually and labelled. All hot or blue nodes will be numbered and their locations indicated. The surgeon must confirm that the specimens are properly labelled before they are sent to pathology.
- The sentinel node pathology requisition will document:
 - 1) The specimen # or letter used when submitting the specimen to pathology.
 - 2) Location of the node basin and level of resection. (*i.e.* SLN #1 right axilla, level 2, SLN #2 right internal

mammary, 2nd intercostal space etc).

- The remaining lymph nodes from a concomitant axillary dissection should be labelled as such and the level of resection denoted (i.e. level I and II axillary dissection etc.)

12- Data Documentation

- Formalized documentation should be included in the patient's clinical record (see attachment for an example).
- Documentation should include the following parameters
 - 1) Initial pre-skin incision count
 - 2) In-vivo SLN count (for each node)
 - 3) Ex-vivo SLN count (for each node)
 - 4) Post excision nodal basin count (after removal of each SLN)
 - 5) Each sentinel node should be labelled numerically or alphabetically, denoting what nodal basin and level they were found and if they were hot or blue stained or both.

PATHOLOGY

- Sentinel nodes will be received by the pathologist in separate containers accompanied by a requisition identifying each SLN by identification number, nodal basin and level. The final pathology report should reflect this information.
- Each sentinel lymph node received will be serially sectioned at 2-3 mm and the whole node will be submitted in total, unless the lymph node has obvious gross tumour, in which case a representative section is sufficient.

Permanent Sections

- Lymph nodes are fixed in 10% buffered formalin.
- Processed and embedded in wax blocks.
- Sectioned as follows:
 - 1) 10 sections cut at 50 micron intervals
 - 2) Levels 1, 5 & 10 stained with H&E (i.e. 3 slides stained with H&E)
 - 3) Level 2 is negative control for the cytokeratin immunohistochemical stain.
 - 4) Level 6 is stained for cytokeratin (immunohistochemistry).
 - 5) Remainder of levels kept unstained for future use if needed

Intraoperative Consultation/Assessment of Sentinel Lymph Node(s)

Institutional feasibility will dictate the facility with which intraoperative assessment may be performed for intraoperative determination of sentinel nodal metastasis. In those institutions so enabled, the following process will occur:

- Size of lymph node. Number of nodes.
- Each node is sliced carefully at a maximum of 2-3mm intervals and note of blue discolouration and gross tumour masses made.
- Single imprint of cut surface of each node made and fixed

in 95% alcohol.

- Rapid H&E stain performed.
- Slide examined for metastases.
- Result phoned to the surgeon in the OR
- In the rare instances where the imprint is suspicious but not diagnostic of malignancy a quick section can be performed to confirm imprint diagnosis. However frozen sections are discouraged because of potential for loss of tissue, fixation artifact, and problems with interpretation of permanent sections including potential interference with immunohistochemistry (Cytokeratin stain).

To summarize, a complete sentinel node assessment includes assessment of: 3 permanent H&E stained slides and a slide with cytokeratin immunohistochemistry for each sentinel node. Intraoperative consultation and imprint histology (touch prep H&E) are optional considerations.

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URLs:

NSABP Protocol B-32: <http://www.nsabp.pitt.edu/B-32.htm>
Radiation Properties: <http://www.princeton.edu/~ehs/radtrain/Modules/basics.html>