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Evidence-Based Series 17-5

A Quality Initiative of the Program in Evidence-Based Care (PEBC, Cancer Care Ontario (CCO)

Sentinel Lymph Node Biopsy in Early-stage Breast Cancer

R. George, M. L. Quan, D. McCready, R. McLeod, R.B. Rumble, and the Expert Panel on SLNB in Breast Cancer

Report Date: July 14, 2009

An assessment conducted December 2013 deferred the review of Evidence-based Series (EBS) 17-5, which means that the document remains current until it is assessed again next year.

EBS 17-5 is comprised of 3 sections and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Surgery page at:
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Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-Based Series 17-5: Section 1

Sentinel Lymph Node Biopsy in Early-stage Breast Cancer: Guideline Recommendations

R. George, M. L. Quan, D. McCready, R. McLeod, R.B. Rumble, and the Expert Panel on SLNB in Breast Cancer.

A Quality Initiative of Cancer Care Ontario's Surgical Oncology Program (SOP) and Cancer Care Ontario's Program in Evidence-Based Care (PEBC)

Report Date: July 14, 2009

This guideline addresses the role of sentinel lymph node biopsy (SLNB) in the surgical management of early-stage breast cancer. The Expert Panel on SLNB in Breast Cancer identified the American Society of Clinical Oncology (ASCO) 2005 guideline on SLNB in early stage breast cancer (1) as a suitable base on which to develop recommendations for Ontario, following an evidence update of the ASCO guideline.

Five questions from the ASCO guideline regarding clinical practice were addressed in this guideline through an updated evidence review. Two additional questions regarding technical aspects of SLNB and how to organize the delivery of SLNB were drafted by the Expert Panel.

QUESTIONS

Clinical Practice

1. Should SLNB be the recommended standard of care for women and men with proven breast cancer, whose clinical presentation is suggestive of early-stage disease?
2. How should the results of SLNB be utilized in clinical practice?
   a. Can level I/II axillary lymph node dissection (ALND) be avoided in patients with negative findings on sentinel lymph node biopsy (SLNB)?
   b. Is level I/II ALND necessary for all patients with positive findings on SLNB?
3. What is the role of SLNB in special circumstances in clinical practice? (special circumstances include large and locally advanced invasive tumours, multicentric tumours, inflammatory breast cancer, ductal carcinoma in situ (DCIS), older age (65 years or more), obesity, male breast cancer, pregnancy, evaluation of the internal mammary nodes, presence of suspicious palpable axillary nodes, prior breast or axillary surgery, and preoperative systemic therapy).
4. What factors affect the success of SLNB (including low rates of complications and false-negative results)?
5. What are the potential benefits and harms associated with SLNB?

Technical Aspects of SLNB

1. What is the recommended mapping technique for SLNB?
2. What operative technique is recommended?
3. What is the recommended technique for pathological processing, handling, and reporting?

Organization of Care

1. How should the delivery of SLNB be organized in Ontario with respect to team membership, experience and training, and the institutional setting?
    a. What is the recommended experience and training for surgeons who perform SLNB?
    b. What are the recommended criteria and resources for institutions performing SLNB?

TARGET POPULATION

The target population for this guideline is all patients, both male and female, with early-stage breast cancer.

INTENDED USERS

The intended users of this evidence-based series are clinicians involved in breast surgery, including surgeons, pathologists, medical oncologists, radiation oncologists, nuclear medicine practitioners, radiologists, other allied health professionals (e.g., nurses, physiotherapists), administrators, and also breast cancer patients.

CLINICAL PRACTICE RECOMMENDATIONS AND EVIDENCE

The following recommendations address the role of sentinel lymph node biopsy in patients with early-stage breast cancer:

***Recommendations** appear in shaded boxes, **Evidence** appears in unshaded boxes.*

SLNB is recommended as the preferred method of axillary staging for all patients with a clinical presentation of early-stage breast cancer in the absence of clinically or pathologically positive lymph nodes

Evidence

Four randomized controlled trials (RCTs) reported high sentinel node (SN) detection rates (95.1%, Sentinella-GIVOM (2,3)) to 97.2%, NSABP B-32 (4) and accuracy (94.4% Sentinella-GIVOM (2) to 97.6%, ALMANAC (5)). False-negative rates were low (e.g., 6.7%, ALMANAC (5)), with the exception of one RCT that had no training component or requirement for use of the blue dye (16.7%, Sentinella-GIVOM (2,3,6)). Node-positive rates were similar in all cases between ALND and any SLNB-alone arms. In the Sentinella-GIVOM non-inferiority trial (2,3,6), there was only one axillary recurrence in 345 SN-negative (SN-) patients at 55.6 months of follow-up, and similar disease-free and overall survival rates. (See Section Two for summaries of the RCTs and the prospective series data.)

ALND (Level I/II) is recommended for:

- Positive results on SLNB (see *Qualifying Statement*)
- Failed SLNB attempts (failure is defined as no localization of a sentinel node)
- Positive results from a needle biopsy of clinically suspicious adenopathy

Evidence

The Expert Panel continues to support full Level I/II ALND for patients that are SN positive (SN+) based on the updated review and the findings of the ASCO Guideline (1). While the

ACOSOG Z0011 trial (7) includes an arm of SN+ patients treated without a completion ALND, no data on treatment-related outcomes were available at the time of this review.

Qualifying Statement

While ALND (Level I/II) is recommended for patients with positive findings on SLNB, exceptions might include:

- Individuals with life-shortening co-morbidities, high perioperative risk, and low risk of residual disease. The decision not to perform Level I/II ALND should be made on a case-by-case basis and ideally in the context of a multidisciplinary case conference.
- High or low risk of residual axillary disease is indicated by several factors, which include: size of primary tumour, size of metastases, absence or presence of extra-nodal extension, lymphovascular invasion, ratio of positive to negative sentinel nodes, and total number of nodes assessed. Online decision aids are available for use that may help in these cases (8).

Evidence

This recommendation is based on the opinion of the Expert Panel.

ALND (Level I/II) is not recommended when the results of SLNB are negative

Evidence

Full ALND can be avoided when SNs are negative on pathologic examination as evidenced by the Sentinella-GIVOM trial (2,3,6), where no statistically significant difference was detected between the SLNB and the ALND group in overall survival (OS) or recurrence-free survival (RFS) at 55.6 months

Preoperative needle biopsy can be performed for clinically suspicious nodes. Patients with a biopsy confirming metastatic disease would proceed directly to ALND, thus avoiding SLNB.

Evidence

This recommendation is based on the opinion of the Expert Panel.

The Role of SLNB in Specific Clinical Circumstances

In general, the SLNB Expert Panel recommends the use (or not) of SLNB in each of the following clinical circumstances, noting that the decision to use SLNB in these circumstances should be individualized for each patient.

Clinical circumstances recommended for SLNB

- T1 or T2 tumours
- Multicentric tumours
- DCIS (with mastectomy)
- Older age*
- Obesity*
- Bilateral breast cancer

Evidence

The majority of patients in the four RCTs reviewed were T1/2, although this was not consistent throughout the trials. The use of SLNB in DCIS with mastectomy is supported by a Standards document (9) and an online Clinical Practice Guideline (10). The recommendations for the use of SLNB with multicentric tumours, older age, obesity, and bilateral breast cancer were based on Expert Panel consensus, a subset analysis from the ALMANAC trial, and results of prospective and cohort series. (see Section 2, pages 19 and 20).

*While SLNB is recommended for both older age and/or obesity, clinicians and patients should be aware that both are risk factors for failed SLN mapping.

Clinical circumstances not recommended for SLNB

- Inflammatory T4 breast cancer

- Prior axillary surgery*

Evidence

All four RCTs reviewed excluded patients with inflammatory breast cancer by not including T4 lesions; the Expert Panel agrees these patients should not be considered candidates for SLNB.
*Two of the RCTs reviewed (ALMANAC (5,11-17) and ACOSOG Z0011 (7)) specifically excluded patients with prior axillary surgery. The Expert Panel agrees that these are not appropriate patients for SLNB but would consider a patient eligible if the previous axillary surgery was a minor operation unlikely to interfere with lymphatic mapping.

Clinical circumstances with inconclusive or inadequate evidence

- Internal mammary lymph nodes*
- Before preoperative therapy*
- T3 or T4 tumours*
- DCIS (without mastectomy)*
- Suspicious palpable axillary nodes*
- After preoperative systemic therapy*
- Prior diagnostic or excisional breast surgery*
- Prior non-oncologic breast surgery*
- Pregnancy**

Evidence

There is insufficient evidence to support or refute the use of SLNB in these settings. The Expert Panel will review new evidence as it becomes available.

* For all of these circumstances, treatment decisions must be made on a case-by-case basis.

** For pregnant patients, there exist concerns about the safety of blue dye, and only small case-series describe its use. Investigational studies suggest acceptable fetal radiation exposures with non-iodine radioisotopes in the dosages used for the sentinel node technique. Additional information and resources can be found on most nuclear medicine speciality society web sites (e.g., The British Nuclear Medicine Society (available at: http://www.bnmsonline.co.uk) [accessed January 9, 2009] (go to "Guidelines and procedures", "Other guidelines", Section 7 of "Notes for the guidance of the clinical administration of radiopharmaceuticals"); The European Association of Nuclear Medicine (available at: https://www.eanm.org/scientific_info/guidelines/gl_onco_sent_node.pdf) [accessed January 13, 2009]). Individual cases must be reviewed with a nuclear medicine specialist. Most Expert Panel members would use the SLNB technique in a pregnant woman beyond the 1st trimester, weighing risk versus benefit on a case-by-case basis.

Factors that Affect the Success of SLNB

Several factors are associated with successful SLNB (defined as low complication and false-negative rates [FNRs]) in all patients.

The SLNB Expert Panel acknowledges that success (defined as low complication and FNRs) is dependent on team experience, case volume, and adherence to established protocols in nuclear medicine, pathology, and surgery and recommends these factors as quality indicators.

Evidence

Evidence from prospective series data show SN detection rates are negatively affected by minimal surgeon training (18-20).
Surgeon experience was found to have a significant effect on SN detection rates (20). A Standards Document recommends that SLNB should only be performed by surgeons who have had proper training in the techniques and who have been audited for performance (9).
Two online Clinical Practice Guidelines stated that SLNB requires a multidisciplinary team and that its success depends on the strengths of the individual components (10,21).

The SLNB Expert Panel recommends the use of periareolar injection technique and combined blue dye and radiotracer protocol (see *Qualifying Statement*).

Evidence

The majority of study protocols incorporated the dual injection technique, as stated in the original ASCO guideline (1), and the Expert Panel continues to endorse this recommendation.

High localization rates are obtained when using a periareolar injection in the meridian of the tumour (22).

Qualifying Statement

The evidence suggests lower localization rates in the obese and in patients who have had a prior lumpectomy

Evidence

One RCT (ALMANAC (5,11-17)) demonstrated that SN detection rates are negatively affected by a high body-mass index (BMI), and the NSABP B-32 trial (4) showed higher FNRs after prior excisional biopsy versus needle biopsy.

Potential Harms and Benefits

Reduced morbidity is the major benefit of SLNB. The panel strongly favours the SLNB technique, which demonstrates less morbidity with equivalent positive node detection rates, compared with ALND.

Benefits

- Less invasive surgery (outpatient procedure and no need for drains)
- Fewer complications (e.g., sensory changes, lymphedema)
- Enhanced pathologic staging

Evidence

The Sentinella-GIVOM (2) trial detected a difference between ALND and SLNB for lymphedema at 12 months, in favour of SLNB, and shorter term benefits in numbness, pain, and arm movement (2,6). For impairment of shoulder function, neither the ALMANAC (5,11-17) nor the Sentinella-GIVOM trial (2,6) detected a long-term difference between the groups. For infection rates, the ALMANAC trial did not detect a difference between the groups. A prospective series that reported on these outcomes detected significant benefits favouring SLNB over ALND for muscle weakness, shoulder stiffness, pain in arm, numbness in breast area, numbness in arm, and strange sensations in arm (all $p<0.05$) (23).

Harms

- Possible allergic reactions to blue dye
- Caution of FNRs
- No long-term survival data

Evidence

In the RCT evidence reviewed, FNRs ranged from 6.7% (ALMANAC (5)) to 16.7% (Sentinella-GIVOM (2,3)), and in the prospective series reviewed, FNRs ranged from 1.9% (24) to 25% (25). The Expert Panel notes that adequate training and technique are required to achieve low FNRs.

Technical Aspects SLNB

A. Mapping Technique

The recommended mapping technique is the dual injection technique with radioisotope and vital blue dye to maximize localization rates.

Evidence

The majority of study protocols incorporated the dual injection technique, as stated in the original ASCO guideline (1), and the Expert Panel continues to endorse this recommendation. High localization rates are obtained when using a periareolar injection in the meridian of the tumour (22).

B. Operative Technique

The Expert Panel recommends using both radioisotope and blue dye for sentinel lymph node

mapping. Using this technique, the incision may be guided by gamma probe readings, allowing the surgeon to identify the sentinel node/s with the probe as well as visually inspect for blue-stained nodes and palpate for clinically suspicious nodes. With the use of the radioisotope, it is also possible to demonstrate that radioactive nodes have been removed by performing ex vivo counts on the resected tissue.

Evidence

This recommendation is based on Expert Panel consensus and is supported by the NSABP B-32 trial protocol (4).

C. Pathology

The recommended pathology technique is that excised sentinel lymph nodes be cut into sections no thicker than 2.0 mm parallel to the longest meridian. This allows for the recognition of small metastatic deposits that might be missed by the examination of a lymph node that has been bivalved. Hematoxylin & Eosin (H/E) staining is routinely employed. While published protocols vary across institutions, all advocate some form of serial sectioning for the evaluation of sentinel nodes.

Evidence

The Expert Panel continues to support the recommendation in Appendix 3 of the 2005 ASCO Guideline (1). Immunohistochemistry (IHC) may be used to help identify very small tumour deposits, but its use is not considered routine.

ORGANIZATION OF CARE RECOMMENDATIONS

Team Recommendation

SLNB should be performed by an experienced team to ensure results equivalent to those obtained with ALND. The proportion of patients successfully mapped correlates with false-negative rates and is a reasonable indicator of quality. Consistent pathology and nuclear medicine protocols need to be adhered to.

Evidence

Patient outcomes should be audited against the current standards of SN detection and FNRs (21,26).

Two online Clinical Practice Guidelines state that SLNB requires a multidisciplinary team (see INTENDED USERS, Section One), and its success depends on the strengths of the individual components (10,21). The Expert Panel also endorses these recommendations.

Surgeon Training Recommendation

The surgeon training recommendation is completion of at least one of the following options for surgeons who perform SLNB:

1. Training during a residency or fellowship program.
2. Mentorship with an experienced surgeon (may include a formal didactic course).
3. Combining the procedure with a number of completion dissections to demonstrate acceptable accuracy (may include a formal didactic course).

The SLNB Expert Panel acknowledges that the training will be different for those surgeons involved with an experienced team versus those with little or no experience.

Evidence

A Standards Document (9) and a Position Paper (26) supported this recommendation, one recommending that SLNB should only be performed by surgeons who have received the proper training in the technique and who have been audited for accuracy (9), and the other recommending that surgeons and team should have taken training followed by a period of self and team audit where success is measured against the outcomes of SN detection rates and FNRs (26). The Expert Panel also endorses these recommendations.

System Recommendations

The minimum system recommendations are that clinicians and patients should have access to:

- a licensed nuclear medicine facility that follows a defined SLNB protocol to perform injection
- a surgeon with:
  - appropriate training and experience in sentinel node detection and extraction
  - access to a hand-held gamma probe, which is used to detect the SN
- a pathologist who assesses the SLN specimens according to a standardized protocol (for examples, see Appendix 3 of the ASCO guideline (1) and the Methods section of the NSABP B-32 trial report (4).

Evidence

These recommendations are supported by the Team and Surgeon Training evidence as well as the protocols of several RCTs (ALMANAC, NSABP B-32). The Expert Panel also endorses these recommendations.

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Evidence-Based Series 17-5: Section 2

Sentinel Lymph Node Biopsy in Early-stage Breast Cancer: Evidentiary Base

R. George, R.B. Rumble, M.L. Quan, D. McCready, R. McLeod, and the Expert Panel on SLNB in Breast Cancer

A Quality Initiative of Cancer Care Ontario's Surgical Oncology Program (SOP) and Cancer Care Ontario's Program in Evidence-Based Care (PEBC)

Report Date: July 14, 2009

This guideline addresses the role of sentinel lymph node biopsy (SLNB) in the surgical management of early-stage breast cancer. The Expert Panel on SLNB in Breast Cancer (Appendix A) identified the 2005 American Society of Clinical Oncology (ASCO) published guideline on SLNB in early stage breast cancer (1) as a suitable base on which to develop recommendations for Ontario, and an update to identify any new evidence was performed.

Five questions from the ASCO guideline regarding clinical practice were addressed in this guideline through the updated evidence review. Two additional questions regarding technical aspects of SLNB and how to organize the delivery of SLNB were drafted by the Expert Panel.

QUESTIONS

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   a. What is the recommended experience and training for surgeons who perform SLNB?
   b. What are the recommended criteria and resources for institutions performing SLNB?

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in Ontario for women, accounting for almost 29% of all female incident cases (2). In Ontario, the guidelines for the surgical management of early-stage invasive breast cancer (3) published in 2005, recommended level I/II axillary lymph node dissection (ALND), a procedure associated with significant permanent morbidity. By contrast, SLNB is a surgical procedure that provides the same diagnostic information for persons with early-stage breast cancer but with less morbidity as compared with level I/II ALND. Observation of the characteristics of blue dye when injected into tissue is the basis for SLNB, as was initially described in the 1920s by Braithwaite (4). The modern concept of using SLN to decide if regional clearance should be done or avoided was articulated by Cabanas in 1977 (5). Due to recent technical developments, SLNB now has widespread use in the surgical management of early-stage breast cancer (1,6). Specifically, the prevalent use of SLNB was suggested in the 2005 ASCO guideline (1), which supported the use of SLNB staging for the majority of females with clinically negative axillas.

Due to the widespread use of SLNB, there are several key issues associated with SLNB when compared with ALND that need to be addressed. These include survival, regional control, morbidity, and accuracy of the procedure (6). Since the 2005 publication of the ASCO guideline (1), new evidence has become available. Cancer Care Ontario's Program in Evidence Based Care's (PEBC) Breast Cancer Disease Site Group (DSG), in conjunction with Cancer Care Ontario's Surgical Oncology Program (SOP), undertook a systematic review of the literature to provide the foundation for an updated 2008 guideline. The purpose of updating the original ASCO 2005 guideline (1) is to determine the efficacy of SLNB when compared with ALND in detection rates, morbidity, and survival. The results of this updated systematic review will be used to help determine if a change in the recommended standard of care for the surgical management of early-stage breast cancer in Ontario should be endorsed.

METHODS

This evidence-based series (EBS) is intended to update the 2005 ASCO guideline (1). The guideline (1) was based on a systematic review of the literature along with Expert Panel consensus. It was evaluated using The Appraisal of Guideline Research and Evaluation (AGREE) Instrument (7). The purpose of the AGREE Instrument is to provide a framework for assessing the quality of the guideline, which includes judgements about the methods used for developing the guidelines, the content of the recommendations, and the factors linked to their implementation. The ASCO guideline (1) was evaluated by two methodologists at the

PEBC and two SLNB Expert Panel members. The results of the AGREE assessment of the ASCO guideline can be found in Appendix B.

Systematic Review

The purpose of this systematic review was to update the 2005 ASCO guideline (1) and re-examine the original recommendations with respect to the additional evidence. The systematic review was performed to obtain evidence to answer the clinical questions.

The clinical practice questions below were adopted from the ASCO guideline for this systematic review. In the results section, the evidence from the systematic review is presented with reference to these questions.

1. How should the results of SLNB be utilized in clinical practice?
   a. Can level I/II axillary lymph node dissection (ALND) be avoided in patients with negative findings on sentinel lymph node biopsy (SLNB)?
   b. Is level I/II ALND necessary for all patients with positive findings on SLNB?
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3. What factors affect the success of SNB (including low rates of complications and false-negative results)?
4. What are the potential benefits and harms associated with SNB?

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (8). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by three members of the Surgical Oncology Program and two methodologists from the PEBC.

This systematic review is a convenient and up-to-date source of the best available evidence on sentinel node biopsy and early-stage breast cancer. The body of evidence in this review is primarily comprised of a clinical practice guideline, meta-analyses, randomized controlled trials (RCTs), and prospective and retrospective non-randomized studies. This evidence forms the basis of the Section 1 recommendations developed by the Breast Cancer DSG and the SOP. The systematic review and the companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

In consultation with the lead author of the ASCO guideline, the ASCO search strategy (detailed in Appendix C) was employed to update the evidence from MEDLINE from 2004 through to the end of May 2008. Search terms used included "sentinel lymph node biopsy", axilla", and "sentinel". These were combined with terms for the disease site including "breast neoplasms" and "breast cancer" (including "breast", "mammary", "ductal" and "cancer", carcinoma", "neoplasm" and "tumor"). Comments, letters, editorials, interviews, lectures, and news publications were excluded, and results were limited to English language publications and reports on humans only. A table of procedural steps detailing the literature search appears in Appendix D. Online conference proceedings from ASCO (2004 through 2008)

and the San Antonio Breast Cancer Symposium (SABCS) (2004 through 2007) were also searched. The Canadian Medical Association (CMA) Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (NGC) (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from these sources were searched for additional trials.

The literature search was updated to current in June 2009. No additional evidence was obtained from the MEDLINE database (June 2008 through May 2009), SABCS Abstracts (2008), the CMA Infobase, or the NGC. Due to the availability of evidence from RCTs, this update, and all future updates to this review, will consider only meta-analyses, systematic reviews, and RCTs.

Study Selection Criteria

Target Population

The target population for this guideline is all patients, both male and female, with early-stage breast cancer.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were one of the following publication types and data comparing SLNB with the standard treatment of ALND was provided:

- Clinical practice guidelines
- Systematic reviews with meta-analyses
- Systematic reviews without meta-analyses
- Randomized Phase III trials
- Randomized Phase II trials
- Non-randomized studies of more than 50 patients to be included if the studies provided a comparative measure (i.e., patient comparison of SLNB to ALND)
- At least one of the outcomes of interest must be reported on

Exclusion Criteria

- Trials published in a language other than English

Synthesizing the Evidence

As none of the evidence obtained in this systematic review was comprised of homogenous data from the RCTs, no pooling was planned or performed.

Quality of the Evidence

The quality of the evidence used to inform recommendations in this guideline are summarized within the narrative for each relevant section.

Outcomes of interest

Evidence was obtained and summarized for SLNB for the following outcomes of interest:

- Success of lymphatic mapping
- False-negative rates
- Negative predictive value
- Overall accuracy

- Recurrence rates
- Recurrence-free survival (RFS) and/or
- Overall survival (OS)

The outcomes of interest were operationalized as follows:

Lymphatic Mapping

To be reported as the percentage of patients for whom lymphatic mapping is successful. When lymphatic mapping is not successful (failed sampling), full ALND is generally necessary to assess the status of the nodes.

False-Negative Rates (FNR)

To be reported as the proportion of patients with negative findings on SLNB who are subsequently found to have disease in the axillary lymph nodes on ALND. An intraoperative false-negative (FN) finding represents a sentinel lymph node that is found to be negative for disease on intraoperative evaluation of frozen section or touch prep but metastasis is detected on evaluation of the permanent section. An axillary false-negative finding is the absence of evident metastasis on evaluation of a permanent section of the sentinel lymph node but findings of metastases by full ALND.

$$\text{FNR} = \frac{\text{False negatives (FN)}}{\text{True positives (TP)} + \text{False negatives (FN)}}$$

Negative Predictive Value (NPV)

To be reported as the proportion of individuals with negative findings of sentinel node biopsy in whom no involvement of the axillary lymph nodes is found on ALND.

$$\text{NPV} = \frac{\text{True negatives (TN)}}{\text{TN+FN}}$$

Overall Accuracy

To be reported as the proportion of patients (positive or negative findings of sentinel node biopsy) for whom the sentinel node biopsy correctly predicts the results of ALND.

$$\text{Accuracy} = \frac{\text{TP+TN}}{\text{Number of patients (N)}}$$

It was planned that where data allow, the FNR, sensitivity, specificity, NPV, and diagnostic accuracy would be re-calculated from the reported values of TP, TN, false positives (FP), and FNs.

Assessment of Study Quality

An assessment of study quality was performed for all the included evidence. For RCTs, items such as randomization, blinding, details of the statistical analysis, the funding sources, the expected effect size and details of the statistical power calculation, length of follow-up, along with any differences in patient characteristics were reported.

For the other evidence types, mostly detailing the diagnostic utility of SLNB compared with ALND, the Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS) tool (9) was used where appropriate. The QUADAS tool is a 14-item questionnaire intended to assess primary studies of diagnostic accuracy for systematic reviews.

For the remainder of the evidence, studies were judged for quality based on full description of patient selection criteria, documentation of interventions, and reporting of outcomes.

Environmental Scan

In addition to the systematic literature search performed to locate indexed evidence to inform the clinical questions, an environmental scan was conducted to locate evidence on the current status of policies, training, techniques, and standards as they relate to the organizational context for the use of SLNB for early-stage breast cancer.

The environmental scan was conducted in January 2008 and involved an extensive examination of material obtained from the World Wide Web using the Google™ (www.google.com) search engine. The environmental scan was conducted by the research coordinator using the following steps:

- Development of keywords and search strategies (identified by the Working Group via teleconference call). Keywords used included terms specifying the procedures (e.g., sentinel lymph node biopsy, SLNB, axillary lymph node dissection, ALND), professional practice terms (e.g., surgeon experience, training), organization and system structure terms (e.g., personnel, surgical volumes, capacity, physical resources), and terms specific to the technical aspects (e.g., type of injection, surgical technique).
- Online searches of non-indexed databases for potentially relevant documents (i.e., professional organizations identified by the Working Group);
- Screening of abstracts to identify research projects for further review (i.e., identified studies from the professional organizations);
- Internet searches for information relevant to the three identified domains, which included targeted and untargeted searches (using the Google search engine).

The SLNB Expert Panel identified the following professional organizations to be reviewed for information relevant to the organizational and systems issues of the guideline:

- American College of Surgeons
- American Society of Clinical Oncology
- American Society of Breast Disease
- American Society of Breast Surgeons
- American College of Radiology
- American Society for Therapeutic Radiology and Oncology
- College of American Pathologists
- Society of Surgical Oncology

The national cancer and guideline agencies were searched in the United Kingdom, Australia, New Zealand, and the United States. Finally, all the Canadian provincial cancer agencies were reviewed and included:

- British Columbia Cancer Agency
- Alberta Cancer Board
- Saskatchewan Cancer Agency
- Cancer Care Manitoba

- Cancer Care Nova Scotia

While the systematic review was primarily performed to obtain evidence related to answering the clinical questions and the environmental scan was primarily performed to obtain evidence related to the organizational questions, the entire body of evidence from both the systematic review and the environmental scan was considered when answering the research questions and in developing the recommendations for this review.

RESULTS

Literature Search Results: Systematic Review

From the MEDLINE search 571 hits were obtained. Based on title and abstract review, 419 of these were excluded, leaving 152 potentially relevant papers that were ordered for full-text review. Of these 152 papers, 68 were determined to be relevant and were retained. The summarized literature search results appear in Tables 1-7 and Appendices E and F.

The National Guidelines Clearinghouse, CMA Infobase, the Cochrane Database of Systematic Reviews, and DARE Abstracts were all searched on August 5, 2008 using the keywords "sentinel" "breast" "SLN" and "SLNB". Eight hits were obtained, but on title and abstract review all were rejected.

Additionally, abstracts from the proceedings of the annual meetings of ASCO (2004 through 2008) and the SABCS (2004 through 2007) were searched on August 5, 2008. Seven abstracts were retained from the SABC and one from ASCO.

Table 1 provides a summary of the literature search results sorted by evidence type. It must be noted that, although a recalculation of the reported outcomes was planned where data would allow, only four papers (10-13) provided the required information. For this reason, the decision was not to recalculate the reported outcomes, as to do so for only four of the 68 included papers could potentially misrepresent the results. As a caveat, readers should be aware that many of the included studies calculated FNR using the total number of patients in the denominator, instead of the sum of false negatives and true positives.

Table 1. Literature search results from the systematic review.

Publication type	Number	References	Table
Clinical Practice Guidelines	1	(3)	-
Systematic reviews with meta-analysis	1	(14)	-
Systematic reviews without meta-analysis	0	-	-
Randomized controlled trials	12 (on 4 RCTs)	(6,15-25)	2, 4-8, Appendix E
Randomized Phase II	0	-	-
Cohort studies	1	(26)	9, Appendix F
Prospective series	39	(10-13,27-61)	3, 10, Appendix F
Prospective audits	1	(62)	Appendix F
Case-control	1	(63)	Appendix F
Retrospective review/audits	11	(64-74)	Appendix F
TOTAL	**68**		

All the obtained papers were fully published except for one of the 12 RCT reports (22) and four of the 39 prospective series reports (11,29,40,47), the single case-control study (63), and one of the 11 retrospective reviews/audits obtained (73), for a total of eight abstracts.

Assessment of Study Quality: RCTs

All the RCTs obtained reported on the exact method of randomization except the ALMANAC trial (15-22), which simply stated that patients were randomized. For the three trials that did report the method of randomization (ACOSOG Z0011, NSABP B-32, and Sentinella-GIVOM), all were appropriate and well described. None of the RCTs reported on blinding, and this is likely due to the difficulties associated with blinding in a surgical trial; although the final statistical analysis could have been blinded to assessors, this was not mentioned. Three of the trials (ALMANAC, ACOSOG Z0011, and Sentinella-GIVOM) were described as being performed according to the intention-to-treat method where patients are analyzed according to which treatment arm they were randomized to regardless of which treatment they actually received. The Sentinella-GIVOM trial was reported as being a non-inferiority design, and the NSABP B-32 was described as being a superiority trial. None of the four RCTs reported any data on withdrawals or losses to follow-up. Three RCTs reported non-industry sources of funding, while the ALMANAC trial reported both government and industry funding. Only the Sentinella-GIVOM trial reported any data on expected effect size and statistical power calculation, likely because this was the only trial based on a non-inferiority design. Only two of the trials (NSABP B-32 and Sentinella-GIVOM) reported on length of follow-up, and due to the shorter follow-up times, neither trial can report any long-term data on disease outcomes. Three trials reported no statistically significant differences between the patient characteristics in either treatment arm, but the ACOSOG Z0011 trial did not report any data on this.

Table 2. Assessment of study quality: RCTs.

Study	Randomization	Blinding	Analysis details*	Funding source	Expected effect size and power calculation details	Length of follow-up (months)	Differences in patient characteristics
ALMANAC	Randomization method not described	NR	ITT, withdrawals and loss to follow-ups NR	Government and industry	NR	NR	No significant differences
ACOSOG Z0011	Computer assisted automated telephone system method	NR	ITT, but withdrawals and losses to follow-up were NR	NCI grant	NR	NR	NR
NSABP B-32	Central randomization using a biased coin minimization algorithm	NR	Superiority trial, withdrawals and losses to follow-up were NR	Government	NR	47.1	No significant differences
Sentinella-GIVOM	Computer assisted telephone-based random permuted blocks stratified by centre method	NR	Non-inferiority trial, ITT, withdrawals and losses to follow-up were NR	Foundation grant	Expected effect size: 6% absolute difference in 5-year DFS (two-sided test, $p<0.05$), $1-\beta=80\%$	55.6	No significant differences

* including intention to treat, study withdrawals, and loss to follow-up.

Note: NR, not reported; ITT, intent-to-treat analysis; NCI, National Cancer Institute; DFS, disease-free survival.

Assessment of Study Quality: Prospective Series

The prospective series reports obtained were consistent in design and in reported outcomes. To assess quality, the QUADAS tool (9) was used. The QUADAS tool is designed to evaluate the quality of diagnostic studies for systematic reviews, and scores quality-related factors as either yes, no, or unclear. While quality scores were mixed, no single study contained enough exceptions to warrant its exclusion. Due to the consistency shown, only exceptions to the desired response of *yes* are detailed in Table 3.

Variations in procedure from the standard SLNB followed by ALND were the following: one study followed a positive SLNB with three-node axillary sampling prior to full ALND if warranted (49), and two followed a positive SLNB with four-node sampling prior to full ALND if warranted (27,36). It should be noted that this had no effect on QUADAS scoring as there is no criterion in the tool capable of capturing this.

Table 3. Assessment of study quality: prospective series.

Criterion	Optimum response (N=39)	Exceptions & references
Q1: Was the spectrum of patients representative of the patients who will receive the test in practice	Yes N=39	-
Q2: Were selection criteria clearly described?	Yes N=27	No: 10 (29,31,32,37,42,44,45,55,56,59) Unclear: 2 (13,48)
Q3: Is the reference standard likely to correctly classify the target condition?	Yes N=37	No: - Unclear: 2 (48)
Q4: Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two test?	Yes N=36	No: - Unclear: 3 (53-55)
Q5: Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	Yes N=21	No: 17 (29,31,37-41,44,45,47,48,50-54,60) Unclear: 1 (55)
Q6: Did patients receive the same reference standard regardless of the index test result?	Yes N=15	No: 21 (27-29,31,32,34,36-39,42,44,45,47,48,50,51,53,54,60) Unclear: 3 (40,55,61)
Q7: Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes N=37	No: - Unclear: 2 (35,55)
Q8: Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes N=25	No: 11 (11,13,40,42,44,45,47,53-55,60) Unclear: 3 (12,29,58)
Q9: Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes N=8	No: 31 (11-13,28-30,32,33,36-48,50,52-60) Unclear: -
Q10: Were the index test results interpreted without knowledge of the results of the reference standard?	Yes N=34	No: - Unclear: 5 (11,12,30,51,61)
Q11: Were the reference standard results interpreted without knowledge of the results of the index test?	Yes N=6	No: 1 (31) Unclear: 32 (11-13,27-30,34-40,42-48,50-53,55-61)
Q12: Were the same clinical data available when the test results were interpreted as would be available	Yes N=34	No: 3 (11,40,55) Unclear: 2 (29,53)

when the test is used in practice?		
Q13: Were uninterpretable/intermediate test results reported?	Yes N=36	No: 2 (11,32) Unclear: 1 (40)
Q14: Were withdrawals from the study explained?	Yes N=36	No: 1 (40) Unclear: 2 (32,53)

Assessment of Study Quality: Other Evidence

One cohort study (26), one prospective audit (62), one case-control (63), and eleven retrospective reports were obtained (64-74). While the results of all of these studies must be interpreted in consideration of the limitations of their designs, all were deemed to be of high enough quality to be included, based on full description of patient selection criteria, documentation of interventions, and reporting of outcomes.

Clinical Practice Guideline

One 2005 CPG was obtained from McCready et al (3). In this CPG one RCT was included comparing SLNB followed by ALND if SN+ with ALND alone in 516 early-stage breast cancer patients with a median follow-up of 46 months. No difference was detected between the groups for OS ($p<0.26$) or other breast cancer events (ipsilateral/contralateral recurrence or regional/nodal metastases) ($p<0.26$). No other outcomes of interest were reported. At the time of publication, the authors acknowledged that SLNB had not yet demonstrated acceptable specificity or sensitivity and recommended that its use be limited to investigational only within the context of a clinical trial. They also recommended that surgeons consider obtaining the training, equipment, and infrastructure to perform SLNB in collaboration with representatives from pathology and nuclear medicine.

Systematic Review with Meta-analysis

One 2006 systematic review with meta-analysis was obtained from Xing et al (14). In this paper, data from 21 studies involving 1273 patients were pooled. The inclusion criteria were that patients had to have operable breast cancer and had to have received neoadjuvant chemotherapy (NAC) prior to SLNB, and all patients had to have received full ALND following SLNB.

Sensitivity values were pooled by dividing the sum of the individual true-positive values by the sum of the individual true-positives plus the false negatives, a technique that cannot account for any heterogeneity between studies. Ninety-five percent confidence intervals (CI) for the pooled sensitivity values were calculated using Diamond's approximation to the exact method for proportion. Meta-analyses were also performed using Bayesian hierarchical methods.

Pooled results were: SN detection rate, 90%; NPV, 90%; accuracy, 94%; sensitivity, 88%; and specificity, 100%.

Randomized Controlled Trial Reports

Thirteen reports (6,15-25,75) were obtained on four ongoing or completed RCTs. All of these reports were published after the 2005 ASCO guideline (1). This section will begin with a brief description of each RCT.

ALMANAC Trial

Eight reports (15-22) were obtained providing results on the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, one in abstract form (22). The ALMANAC trial did include males in the study population, but excluded multicentric cancer, previous ipsilateral breast or axillary surgery, previous RT to ipsilateral breast of axilla, and pre-existing limb disease. The ALMANAC RCT was completed in two phases: a validation

phase to measure aspects of the learning of this newer procedure and a randomized phase where SLNB→ALND was compared with the standard treatment of ALND. Outcomes for these two phases are reported separately.

Validation Phase

Two of the papers reported outcomes obtained during the validation phase of the trial (19,21). The trial schema for the validation phase was as follows (Fig. 1):

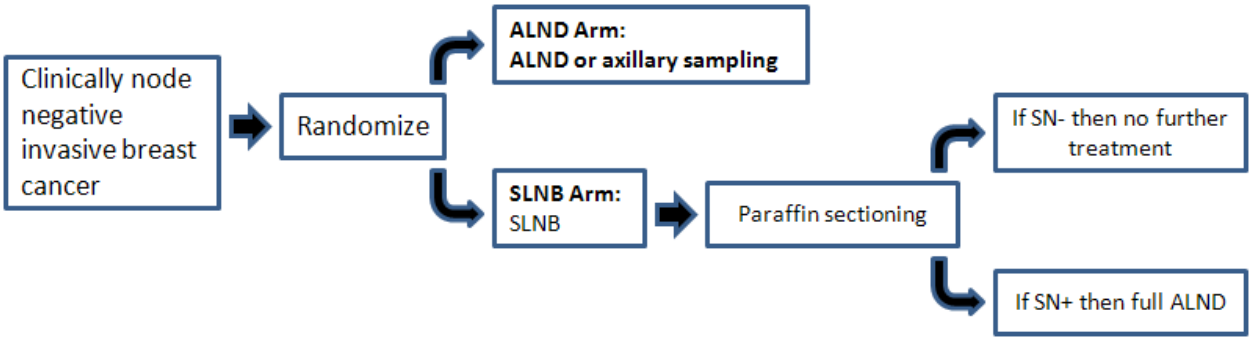
Figure 1: Trial schema for ALMANAC Trial, validation phase.

The most recent validation phase paper (19) reported an SN detection rate of 96%, an FNR of 6.7%, diagnostic accuracy of SLNB of 97.6%, and a sensitivity of 93.3%. Other reported findings were factors associated with mapping failure (high BMI, tumour located outside the upper outer quadrant, and non-visualization of the SN on lymphoscintigraph), and factors associated with FNs (high tumour grade and low number of SNs harvested).

Randomization Phase

Five of the obtained papers reported on randomization phase outcomes (15-18,22). The trial schema for the randomized phase was as follows (Fig. 2):

Figure 2: Trial schema for ALMANAC Trial, randomized phase.



The most recent results available on the randomization phase reported an SN detection rate of 96%, and an FNR of 3% (17). One paper, by Fleissig et al (16), reporting on the results of the Trial Outcome Index (TOI), detected significant benefits ($p<0.05$) favouring SLNB at all time points (1, 3, 6, and 18 months). The report by Goyal et al (22) found no significant differences between SLNB then ALND (SLNB→ALND) and ALND for lymphedema, sensory loss, intercostobrachial nerve division rates, impairment of shoulder function, infection rate, or time to resumption of normal duties. This same report detected significant differences ($p<0.05$) between SLNB→ALND and ALND for median operative time to completion for two-step ALND (33 minute [min.]) versus one-step ALND (22 min.) and the total median axillary operative time, two-step ALND (53 min.) versus one-step (22 min.), and hospital length of stay, two-step ALND (10 days) versus one-step ALND (6 days). One report (15) stated that the

results obtained do not support a learning curve for SLNB but noted that success was dependent on localization of the SN and proper pathologic analysis of the SN.

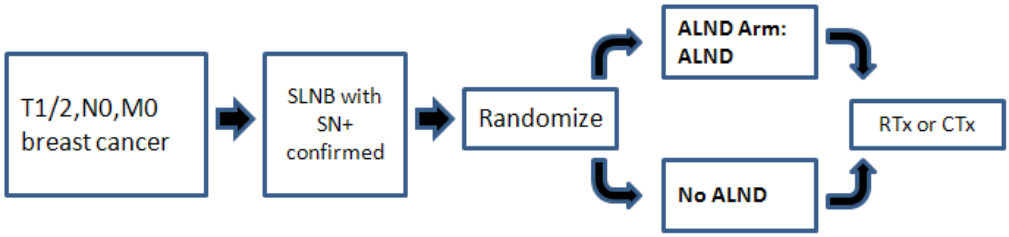
Subgroup Analysis

One additional paper (20) reported on a subgroup analysis of the 75 patients that entered the trial with a multicentric disease that was unknown at study entry. This single paper reported on a subgroup analysis comparing outcomes for unifocal versus multifocal disease and did not detect a difference between the two disease types for SN detection rates, accuracy, sensitivity, or NPV; however, a statistically significant difference was detected for FNR, favouring unifocal disease (p=0.05).

ACOSOG-Z0011 Trial

One report (23) on the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was obtained. Results of the previous ACOSOG Z0010 trial appear in Appendix E (52). The ACOSOG Z0011 study was an RCT comparing SLNB with and without ALND in a population of women with SN+ T1/2N0M0 breast cancer. This trial was closed early (2004) due to poor accrual. The trial schema for ACOSOG Z0011 was as follows (Fig. 3):

Figure 3: Trial schema for ACOSOG Z0011 Trial.

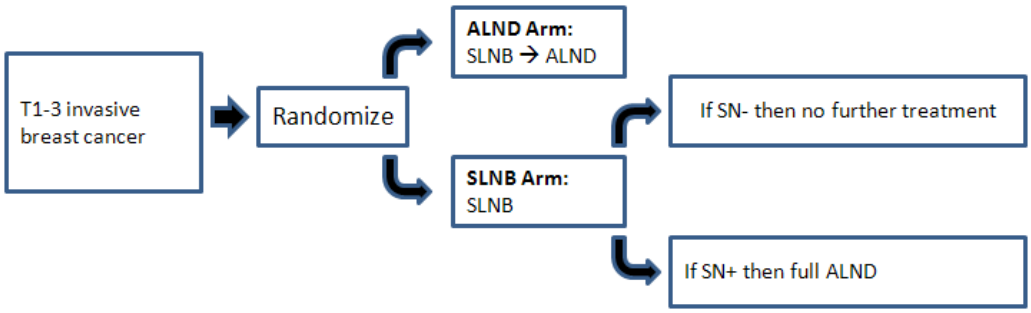


While not reporting on any of the main outcomes of interest, Lucci et al did provide data on other results, and significant benefits favouring SLNB over ALND were detected for infection (p<0.05), axillary seroma (p<0.0001), and axillary paresthesias (p<0.05).

NSABP B-32 Trial

One report on the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial (6) was obtained. The NSABP B-32 study was an RCT comparing SLNB with and without ALND in a population of women with resectable invasive adenocarcinoma of the breast. The trial schema for NSABP B-32 was as follows (Fig. 4):

Figure 4: Trial schema for NSABP B-32 Trial.

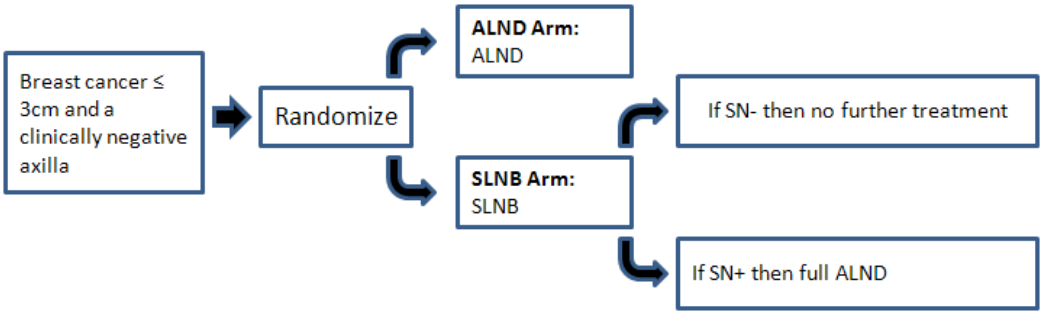


Krag et al (6) reported an SN detection rate of 97.2%, FNR of 9.8%, accuracy of 97.1%, and a sensitivity of 90.2%. Factors associated with higher FNRs were tumour region (FNRs, lateral: 11.8%; medial, 9.1%; central, 5.5%; p<0.04), biopsy type (excisional or incisional, 15.3%; fine-needle aspiration or core, 8.1%; p<0.0082), and number of specimens removed during SLN resection (SLNs removed: one, 17.7%; two, 10%; three, 6.9%; four, 5.5%; five or more, 1.0%).

Sentinella-GIVOM Trial

Three reports on the Sentinella-GIVOM trial (24,25,75) were obtained. The Sentinella-GIVOM study was an RCT comparing SLNB and ALND with SLNB and ALND only if SN+. The trial schema for Sentinella-GIVOM was as follows (Fig. 5):

Figure 5: Trial schema for Sentinella-GIVOM Trial.



The paper by Zavagno et al (24) reported an overall SN detection rate of 95% (SLNB: 95.1%, ALND: 95.9%), FNR of 16.7%, accuracy of 94.4%, sensitivity of 83.3%, and a specificity of 100% (ALND arm). This same paper reported locoregional recurrence rates of 4.6% (SLNB) versus 0.85% (ALND), RFS of 87.6% (SLNB) versus 89.9% (ALND) (p= nonsignificant [n.s.]), and OS rates of 94.8% (SLNB) versus 95.5% (ALND) (p=n.s.). The incidence of axillary recurrence in the sentinel node biopsy arm was one of 345 and none of 352 in the ALND arm. Significant benefits favouring SLNB were detected for lymphedema rates, restriction of shoulder mobility, numbness, and preoperative Psychological Global Well-Being Index (PGWBI) scores (all p<0.05). No difference was detected between SLNB and ALND for Health-Related Quality of Life (HRQoL) or Short Form (SF)-36 Health Survey scores. Another report by the same authors (25) stated that FNR was associated with multiple axillary node involvement (p=0.018). It should be noted that the primary endpoint of detecting clinical equivalence in disease-free survival (DFS) was not attained. The Kaplan-Meier five-year DFS results were 89.9% (95% CI, 85.3% to 93.1%) ALND and 87.6% (95% CI, 83.3% to 90.9%) SLNB, a difference of 2.3% (95% CI, -3.1% to 7.6%; p=0.7692) (24). The upper boundary of 7.6% did exceed the stated acceptable difference of 6%, and the authors of that report concede the possibility that DFS could indeed be worse in the SLNB arm (24). However, this may be explained by the fact that the Trial Committee was forced to stop enrolment near the halfway mark (enrolled 749 out of an anticipated 1498) due to patients refusing randomization into the ALND arm, which affected the trial's statistical power calculations.

Randomized Controlled Trial Details

Table 4 details the outcomes that were reported in each publication. As two of the RCTs (ALMANAC, Sentinella-GIVOM) had multiple publications with varying outcomes, only the most recent data available were used, where appropriate.

Table 4. RCT study details.

Study	Authors	Outcomes reported
ALMANAC	Goyal et al, 2005 (21)	*Validation phase report* • Diagnostic utility • Special circumstances
	Goyal et al, 2006 (19)	*Follow-up validation phase report* • Diagnostic utility • Special circumstances • Benefits/harms
	Clarke et al, 2004 (15)	*Randomization phase report* • Diagnostic utility • Special circumstances • Learning curve for SLNB data
	Goyal et al, 2004 (17)	*Randomization phase report* • Diagnostic utility • Special circumstances
	Fleissig et al, 2006 (16)	*Randomization phase report* • Special circumstances • Trial Outcome Index (TOI)
	Goyal et al, 2006 (22)	*Randomization phase report* • Special circumstances • Benefits/harms
	Goyal et al, 2008 (18)	*Randomization phase report* • Special circumstances • Benefits/harms
	Goyal et al, 2004 (20)	*Randomization phase report* • Special circumstances • Multicentric versus unifocal tumours
ACOSOG Z0011	Lucci et al, 2007 (23)	• Benefits/harms
NSABP B-32	Krag et al, 2007 (6)	• Diagnostic utility
Sentinella-GIVOM	Del Bianco, 2008 (75)	• Benefits/harms
	Zavagno et al, 2008 (24)	• Diagnostic utility • Therapeutic outcomes • Benefits/harms
	Zavagno et al, 2008 (25)	• Diagnostic utility • Therapeutic outcomes • Benefits/harms

Table 5 details the indication, the total number of patients involved, the comparisons made, the exclusion criteria, and any of the special clinical circumstances that were reported in any of the RCT reports. All four RCTs included patients with early breast cancer with no clinically detectable nodal involvement. The ALMANAC and NSABP B-32 trials both compared an arm of SLNB followed by full ALND with another arm that only performed ALND if a positive sentinel node was detected. The ALMANAC trial added the option of replacing full ALND with radiation therapy (RT) if warranted. The ACOSOG Z0011 trial included all SN+ patients allocated to one of two available treatments, ALND with either CT or RT compared with CT or RT alone. The NSABP B-32 trial compared full ALND following SLNB for all patients with ALND following SLNB only for patients with positive nodes. Trial schemas are presented within the discussion for each of the individual RCTs. Exclusion criteria in the four RCTs were similar but inconsistent. Regarding special clinical circumstances, while none of the RCTs excluded males from the study population, only the ALMANAC trial reported the number of males included in the study population.

Table 5. RCT study details.

Study	Indication	Total N	Comparisons	Exclusion criteria	Special circumstances reported on
ALMANAC trial (16)	Clinically node negative invasive breast cancer	1031	SLNB→ALND or RT (if SN+) *versus* ALND alone	• Multicentric cancer • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast of axilla • Pre-existing limb disease	Males were included
ACOSOG Z0011 Trial (23)	T1/2,N0,M0 breast cancer with SN+ confirmed	891	ALND+RTorCT *versus* RTorCT	• Previous cancer within 5 years • Bilateral breast cancer • Multicentric disease • Three or more positive SNs • Gross extracapsular invasion • Matted nodes at SLND • Contraindications to ALND • Any risk factor precluding future treatment	N/A
NSABP B-32 Trial (6)	T1-3 invasive breast cancer	5611	SLNB→ALND *versus* SLNB→ALND if SN+	NR	N/A
Sentinella-GIVOM (24)	Breast cancer ≤ 3cm and a clinically negative axilla	749	SLNB→ALND (if SN+) *versus* ALND alone	• Non-palpable tumours • multiple tumours • DCIS • tumours >3cm • clinically positive axilla • distant metastases • previous neoadjuvant therapy	N/A

Note: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RT, radiotherapy treatment; SN+, positive sentinel nodes; RT, radiotherapy; CT, chemotherapy treatment; DCIS, ductal carcinoma *in situ*.

Randomized Controlled Trial Outcomes

Table 6 reports the diagnostic utility outcomes for the three RCTs providing that data. Reported SN detection rates ranged from 95% (Sentinella-GIVOM) to 97.2% (NSABP B-32), FNRs ranged from 6.7% (ALMANAC) to 16.7% (Sentinella-GIVOM), accuracy ranged from 94.4% (Sentinella-GIVOM) to 97.6% (ALMANAC), and sensitivity ranged from 83.3% (Sentinella-GIVOM) to 93.3% (ALMANAC). Only the Sentinella-GIVOM trial reported on specificity (100%). The ACOSOG Z0011 Trial (23) did not report on any diagnostic utility outcomes.

Table 6. Diagnostic utility outcomes reported in RCT publications.

Study	Diagnostic utility outcomes				
	SN detection rate %	FNR %	Accuracy %	Sensitivity %	Specificity %
ALMANAC trial (19)	96.1 (803/836)	6.7 (19/282)	97.6 (782/803)	93.3 (263/282)	NR
NSABP B-32 Trial (6)	97.2 (5379/5536)	9.8 (75/766)	97.1 (2544/2619)	90.2 (691/766)	NR
Sentinella-GIVOM (24)	95.0 Overall (629/662) 95.1 SLNB (630/662) 94.9 ALND (all) (628/662)	16.7 (18/108)	94.4 (305/323)	83.3 (90/108)	100 ALND (all)

Note: NR, not reported; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 7 details treatment-related outcomes, reported only by the Sentinella-GIVOM trial. This trial detected no difference between the ALND arm and the SLNB arm for overall OS or RFS. Only one patient in the SLNB arm of the trial had an axillary recurrence with follow-up complete to 55.6 months. The ALMANAC, ACOSOG Z0011, and NSABP B-32 trials did not report on any treatment-related outcomes.

Table 7. Treatment-related outcomes reported in RCT publications.

Study	Treatment-related outcomes	
	Overall survival %	Recurrence free survival %
Sentinella-GIVOM (24)	94.8 SLNB 95.5 ALND p=ns	87.6 SLNB 89.9 ALND p=ns

Note: NR, not reported; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.
*Author's calculation.

Table 8 details the benefits and harms, reported by three of the four RCTs. For lymphedema, the ALMANAC trial did not detect a difference between the two arms when SLNB is followed by ALND, while the Sentinella-GIVOM trial did at 12 months, in favour of SLNB arm. For sensory loss, the ALMANAC trial did not detect a difference, while the ACOSOG Z0011 trial detected a difference favouring ALND at 12 months ($p<0.05$) when compared to a completion dissection after SLNB, and the Sentinella-GIVOM trial detected a difference favouring SLNB at 12 months ($p=0.004$). For intercostobrachial nerve division rates, the ALMANAC trial did not detect a difference between the SLNB and ALND arms. For impairment of shoulder function, neither the ALMANAC nor Sentinella-GIVOM trial detected a difference between the groups. For infection rates, the ALMANAC trial did not detect a difference between the groups, while the ACOSOG Z0011 trial detected a statistically significant difference in favour of ALND when compared to SLNB followed by ALND ($p<0.05$). For time to resumption of normal duties, the ALMANAC trial did not detect a difference between groups. For pain, the Sentinella-GIVOM trial did not detect a difference between the groups at 12 months ($p=0.33$) but did show post-surgery improvements in pain, numbness, and arm movement.

Overall, the benefit was afforded those who were able to avoid ALND. Patients who had SLNB followed by ALND had similar results to ALND alone (e.g., ALMANAC trial, see Table 8 below), with the possible exceptions of sensory loss and infection, detected only in the ACOSOG study (Table 8). The NSABP B-32 trial did not report on any benefits or harms.

Table 8. Benefits and harms reported in RCT publications.

Study	Lymphedema	Sensory loss	Inter-costobrachial nerve division rates	Impairment of shoulder function	Infection rate	Time to resumption of normal duties	Pain	Hospital length of stay
ALMANAC trial (22)	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	NR	10d SLNB→ALND *versus* 6d ALND, p<0.05
ACOSOG Z0011 Trial (23)	NR	12 months: 39% SLNB+ALND versus 9% ALND, p<0.05	NR	NR	8% SLNB+ALND versus 3% ALND, p<0.05	NR	NR	NR
Sentinella-GIVOM (75)	12 months: OR: 0.37 (SLNB/ALND), p=0.005*	12 months: OR: 0.53 (SLNB/ALND), p=0.004*	NR	12 months: OR: 0.73 (SLNB/ALND), p=0.33* (arm movement)	NR	NR	12 months: OR: 0.76 (SLNB/ALND), p=0.30*	NR

Note: NR, not reported; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; OR, odds ratio.
* Note that 36% of all randomized to the SLNB arm were found to be SN+ and received ALND.

Cohort Studies

One paper reporting on a cohort study was obtained (26). See Table 9 for details.

Table 9. Cohort study details.

Study	Indication	Comparison	Outcomes
Rietman et al, 2004 (26)	SI/II breast cancer	ALND, SLND with SN+ (N=138) SLND with SN- only (N=66)	Statistically significant benefits detected on the following outcomes in favour of SLNB at 12 months (all p<0.05): • Pain • Numbness • Forward flexion • Abduction/external rotation • Strength of shoulder abductor • Strength of elbow flexors • Grip strength • Circumference of upper arm • Circumference of forearm • SDQ (0-100) • GARS (18-72)

Note: ALND, axillary lymph node dissection; SLND, sentinel lymph node biopsy; SN, sentinel node; SDQ, Shoulder Disability Questionnaire; GARS, Groningen Activity Restriction Scale.

Prospective Series

Thirty-nine papers reporting on prospective series were obtained (10-13,27-61,65,76). Four of these papers were available in abstract form only (11,29,40,47), the remainder were fully-published.

Outcomes and results are reported in Table 10 below. Three papers reported outcomes on lymphatic mapping success (10,31,48). Twenty-five papers reported SN detection rates (10-13,27-30,32,34,35,38,40,41,43,44,46,47,51,53,55,57,58,60,61), with results ranging from a low of 77.6% (in the NAC group) (43) to 100% (47). The paper by Intra

et al (38) reported an SN detection rate of 1.4%, but this was due to all patients in the study having DCIS. Thirty of the papers obtained reported outcomes on FNR (10-13,27,28,30-37,39-41,43-46,48,50,53,55-58,60,61). The majority of results fell between 5% and 15%. Ten of the papers reported outcomes on NPV (10,13,35,36,41,43,46,47,49,57), nine reported outcomes on accuracy (10,13,40,41,43,46,49,53,60), and fourteen reported outcomes on sensitivity (10,13,27,28,34,36,41,45-49,57,60), with the low of 34% being found with hematoxylin-eosin (H/E) plus cytokeratin immunostain (45). Five of the obtained papers reported on specificity (13,45,46,49,60) and five reported outcomes on recurrence rates (35,38,42,48,59). Konstantiniuk et al (42) found no difference between SLNB and ALND for local, axillary, or distant recurrence. Intra et al (38) reported a 25% recurrence rate in the SN+ group. Two of the obtained papers reported outcomes for RFS (35,42). Gimbergues et al (35) reported a 91% overall RFS. Konstantiniuk et al (42) reported a 95% RFS in the SLNB group and an 89.4% RFS in the ALND group (p=n.s.). Two of the obtained papers reported outcomes on OS (35,42). Gimbergues et al (35) reported a 97% OS. Konstantiniuk et al (42) reported a 97.2% OS in the SLNB group and an OS of 94.8% in the ALND group (p=n.s.).

The following factors were associated with a failed SN detection: minimal surgeon training (12,52,57), extracapsular tumour involvement (28), high BMI (28,52), and increasing age (35,52,58). The following factors were associated with FNR: presence of multifocal tumours (30,58), larger tumour size (12,28), upper outer quadrant tumour location (12), removal of a single SN (12), identification of a single positive SN (12,33), use of Immunohistochemistry (IHC) (12), and inadequate radioactive ratio (33). One of the obtained papers detected significant benefits favouring SLNB over ALND for muscle weakness, shoulder stiffness, breast area numbness, and pain, numbness, or strange sensations in an arm (all $p<0.05$) (54).

Table 10. Prospective series report summaries.

Outcome	Number of papers	Min:Max (%) Median (%)
Lymphatic mapping success	3 (10,31,48)	87.3 (31): 99 (48) Median: 94.5 (10)
SN detection rates	25 (10-13,27,29,30,32,34,35,38,40,41,43,44,46,47,51,53,55,57,58,61)	77.6 (43): 100 (47) Median: 94.3 (10)
FNR	30 (10-13,27,28,30-37,39-41,43-46,48,50,53,55-58,60,61)	1.9 (10): 25 (2,13) Median: 5.6 (32,53)
NPV	10 (10,13,35,36,41,43,46,47,49,57)	61.5 (13): 98.4 (36) Median: 93.2 (93.1 (49), 93.3 (41))
Accuracy	9 (10,13,40,41,43,46,49,53,60)	67.9 (13): 100 (60) Median: 97.5 (53)
Sensitivity	14 (10,13,27,28,34,36,41,45-49,57,60)	34 (45): 100 (27,34,36) Median: 89.6 (87.5 (49), 91.6 (57))
Specificity	5 (13,45,46,49,60)	100 (13,45,46,49,60) Median: 100
Recurrence rates	5 (35,38,42,48,59)	0.5 (48): 6.5 (59) Median: 1.6 (59)
RFS	2 (35,42)	89.4 (ALND) (42): 95 (SLNB) (42)
OS	2 (35,42)	94.8 (ALND) (42): 97.2 (SLNB) (42)

Note: SN, sentinel node; FNR, false-negative rate; NPV, negative predictive value; RFS, recurrence-free survival; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; OS, overall survival.

Prospective Audit

One paper reporting on a prospective audit was obtained (62). In this paper, the reported SN detection rate was 100% in the SLNB group and 90% in the ALND group. This difference may have been the result of four T4 patients entering the study, all in the ALND group, but definitive data are unavailable. In both groups, the recurrence rate was 0.8% with a 46-month minimum follow-up.

Case-Control Studies

One paper, available in abstract form only, was obtained that reported on a case-control study comparing SLNB followed by full ALND with (cases) and without (controls) neoadjuvant CT (63). Statistically significant differences were found between cases and controls for SN detection rates (91.3% cases vs. 99.1% controls, p=0.01), FNR (23.8% cases vs. 5.9% controls, p=0.05), and accuracy (88.1% cases vs. 98.1% controls, p<0.01).

Retrospective Reviews

Eleven papers reporting on retrospective reviews were obtained (64-74). All were fully published except for the 2007 paper by Soler et al (73).

The SN detection rates reported in the retrospective studies obtained ranged from 91.1% (72) to 98.9% (73). Reported FNRs ranged from a low of 5% (67) to a high of 16.6% (65). Three of the papers (67,71,73) reported data on recurrence rates: 4.1% SLNB vs. 6.1% SLNB+ALND, p=NR (67); 2% SLNB vs. 0.4% ALND, p=0.004 (71) and 0% SLNB vs. 1% SLNB+ALND, p=NR (73). Two of the papers (69,72) reported on OS: 100% SLNB vs. 97% ALND, p=NR (72) and 89% SLNB vs. 85% ALND, p=0.026 (69).

Special Circumstances

RCT Evidence

The reports on the ALMANAC trial (15-22) included data on two special circumstances. Males were included in this trial, and comprised four of the 618 included patients. As the trialists did not expect results for males would be different from females, outcomes were not reported separately. The paper reporting the subgroup analysis comparing unifocal tumours with multifocal tumours found no difference between the two groups for SN detection, accuracy, sensitivity, or NPV but did detect a significant difference favouring unifocal tumours for FNR. None of the other RCTs provided data on any of the special circumstances.

Cohort Studies

The cohort study (26) did not report on any of the special circumstances.

Prospective Series

Twelve of the prospective series papers obtained reported on special circumstances (11,29,32,35,38,40,41,43,46,47,50,60,61).

Five prospective series papers included results for DCIS patients (38,41,47,50,60). SN detection rates for these five papers were from 100% (47), 96.2% (60), and 91.5% (41) to the low of 1.4% in the paper by Intra et al (38), which only included DCIS patients. Two of these papers reported FNRs of 4.1% (50) and 4% (41).

Four papers included results on patients that received neoadjuvant chemotherapy (NAC) (11,35,43,61). SN detection rates for three of these papers were 93.8% (35), 93.5% (11), 90% (61). The paper by Lee et al (43) comparing NAC with no NAC in a group of patients that received SLNB→ALND (if SN+) detected a statistically significant difference in SN

detection rates favouring no NAC (97% no NAC vs. 77.6% NAC, p<0.05). FNRs ranged from a low of 5% (61) to 14.3% (35). The paper by Lee et al (43) found no difference between the NAC and no NAC groups for FNR (5.6% NAC vs. 7.4% no NAC, p=n.s.). The study by Gimbergues et al (35), in which 100% of all included patients received NAC, reported an SN detection rate of 93.8% and an FNR of 14.3%.

Three papers included results on patients that had multifocal (29,40) or multicentric disease (41). Two of these papers reported SN detection rates of 99% (29) and 91.5% (41). Knauer et al (41) reported an FNR of 4%, and Kim et al (40) detected no significant differences between unifocal and multifocal disease for SN detection, FNR, or accuracy.

One paper reported results on a study including male patients (46). The reported SN detection rate was 94.3%, and the FNR was 6.3%. Another paper reported results on a study including patients with prior ipsilateral breast or axilla surgery (32). The reported SN detection rate was 95%, and the FNR was 5.6%.

Prospective Audit

Neither the prospective audit (62) nor the case-control study (63) reported on any of the special circumstances.

Retrospective Studies

Of the 11 retrospective study reports obtained, only the paper by Soran et al (74) included any data on special circumstances. In this study involving 1500 breast cancer patients, 66.8% were diagnosed with infiltrating ductal cancer, and 10.5% were diagnosed with multicentric tumours. Outcomes were not reported separately for these patient subgroups.

Environmental Scan

As previously described, an environmental scan was conducted to locate evidence on the current status of policies, training, techniques, and standards as they relate to the organizational context for the use of SLNB for early-stage breast cancer.

Table 11 details the evidence located through the environmental scan. Five sources were retained (77-82) on the basis of their relevance, currency, and applicability, following review by the working group. One of the evidence sources obtained was a standards document (79), one was an assessment report (80), one was a position paper (81), and two were guidelines available online only (78,82) (see Table 10 for results).

Table 11. Environmental Scan results

<table>
<tr><th>Author
year (ref)</th><th>Title, evidence</th></tr>
<tr><td>Health Information and Quality Authority 2006 (79)</td><td>National Quality Assurance Standards for Symptomatic Breast Disease Services: Developing Quality Care for Breast Services in Ireland

Standard: all patients with invasive disease should have axillary staging.
<table>
<tr><td>Quality objective:</td><td>accurate staging of the axilla</td></tr>
<tr><td>Outcome measure:</td><td>histopathologic assessment of axillary lymph node</td></tr>
<tr><td>Target:</td><td>>90% of all cases</td></tr>
</table>
• This goal can be achieved in multiple ways: sentinel node mapping with blue dye and isotopes, level I/II/III ALND
• SLNB should only be done by surgeons with proper training in the technique that have been audited for accuracy in at least 30 cases
• Where SLNB detects SN+, axillary treatment should include level I/II/III ALND</td></tr>
</table>

	• When lymphatic mapping detects the SN in the internal mammary chain, removal of that node should be considered. Special Circumstances: DCIS: SLNB is recommended in patients with extensive, high-grade or associated disease with a palpable mass Histopathology: The SLN sample should be sliced at no more than 0.2cm intervals and submitted for microscopic evaluation in its entirety
MSAC Assessment Report 2005 (80)	*Sentinel Lymph Node Biopsy in Breast Cancer* Diagnostic Accuracy: Pooled SN detection rate: 94.1% (192 studies) Pooled FNR: 4.7% (130 studies) Effect of team experience on Diagnostic Accuracy: There is no evidence to support or refute a training effect on diagnostic accuracy Effect of protocol variables on Diagnostic Accuracy: Detection rates were higher and FNR's were lower when a combination of dye and radioisotopes were used as a tracer when compared with dye only Effect of tumour/patient variables on Diagnostic Accuracy: Neither tumour size nor palpability have an effect on detection or FNRs Special Circumstances: NAC contributes to significantly higher FNRs in women compared with no NAC. No difference has been detected between NAC/no NAC in SN detection rates. Safety: Complication rates (e.g. infection, lymphedema) are significantly lower for SLNB compared with either ALND or SLNB → ALND. Effectiveness: There is insufficient evidence to assess the impact of SLNB on long-term survival. One RCT detected no difference between SLNB and SLNB → ALND for both recurrence and OS after a median follow-up of 46 months. Cost-effectiveness: Results of a cost-minimization analysis using recurrence and OS as effectiveness outcomes: • 100 SLNB procedures: AUS$251,942 → $514,277 • 100 ALND procedures: AUS$325,185 → $499,600 • 100 SLNB+ALND (if SN+): AUS$280,203 → $590,097
Royal Australasian College of Surgeons Breast Section 2005 (81)	*NBCC position statements: Sentinel node biopsy in breast cancer* • Surgeons and team should have taken an educational program followed by a period of self/team audit • Outcome measures should be by SN detection rate and FNR (where FNR is calculated following Level 2 ALND) Current standards are: • SN detection rate: >90% in 20 consecutive cases • FNR: 5-15% • Use of SLNB in patients with larger (T2/3) and multifocal tumours should be

	considered investigational • Use of SLNB in patients with DCIS should also be considered investigational • The standard of care for SLNB SN+ patients remains Level 2/3 ALND
NCCN (US) 2008 (82)	*NCCN Practice guidelines in oncology* Invasive breast cancer: all patients with T1/2A/2B invasive breast cancer should be considered candidates for SLNB, the preferred method of lymph node staging. Special Circumstances: DCIS: [Category 2A recommendation]: total mastectomy with or without SLNB, with or without reconstruction.

British Nuclear Medicine Society
2007 (78)
	Procedure Guidelines for Radionuclide Lymphoscintigraphy for Sentinel Node Localisation in Breast Carcinoma
	
	Indications:
	SLNB is recommended in patients (where there is no clinical evidence of either nodal or distant metastases):
	• With T1/2 invasive breast carcinoma
	• With high-risk or microinvasive DCIS
	• With good prognostic group tumours (tubular, medullary, mucinous, papillary)
	• Following primary CT
	• SLNB should be considered an option for patients with larger tumours (T3) as long as there is no evidence of metastases.
	
	Contraindications:
	• Regional or distant metastases
	• Previous surgery or RT to tumour site or ipsilateral axilla
	• Known allergy to dye or radiocolloid
	• Patient unwilling to have ALND if SN+
	
	Sources of SN detection failure:
	• Skin contamination
	• Operative position different from patient position when overlying skin is marked
	• Differentiation of SLN from sites of lymphatic hold-up
	• Differentiation of SLN from second-tier nodes
	• Failure to locate SLN accurately if relying on images in one plane only
	• Failure to locate low-count SLNs
	• Incorrect or failure of communication of report to surgical team
	• Apparent non-drainage: associated with higher chance of aberrant SLN and of metastases to SLN
	
	Outcome analysis:
	• SLNB requires a multi-disciplinary team and its success depends on the strengths of the individual components. All patients should be reviewed in a multi-disciplinary team meeting.
	• Patient outcomes should be regularly audited against current standards
	• The accuracy of the technique can be assessed by the proportion of patients whose SLNs contain metastases, which should match that of axillary clearance and the % of patients with clear SLNs who develop recurrent disease early (false negatives)
	• Recommended standards are:
	  • SN detection rate should be > 95% patients
	  • 20 – 30% SLN's should contain metastases, depending on patient

	population/tumour size • FNR should be < 5%

Note: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; SN, sentinel node; +, positive; DCIS, ductal carcinoma in situ; FNR, false-negative rate; NAC, neoadjuvant chemotherapy; RCT, randomized controlled trial; CT, chemotherapy; RT, radiotherapy.

Environmental Scan Results: Indications

All patients presenting with T1/2A/2B invasive breast cancer (78,82) and with good prognostic tumours (tubular, medullary, mucinous, papillary) (78) should receive SLNB. All patients should be reviewed by a multidisciplinary team (78).

Environmental Scan Results: Contraindications

The following factors are considered contraindications to SLNB: regional or distant metastases, previous surgery or RT to tumour site or ipsilateral axilla, known allergy to dye or radiocolloid, and patient unwilling to have ALND if SN+ is detected (78).

Environmental Scan Results: Follow-up

Where SN+ is detected ALND should be performed (79,81).

Environmental Scan Results: Lymphatic Mapping Success

Mapping can be done with either blue dye alone or in combination with radioisotopes (79). When SN mapping detects the SN in the internal mammary chain, removal of that node should be considered (79).

Environmental Scan Results: SN Detection Rates

The current reported standard for SN detection rates is greater than 90% (81) to greater than 95% (78). Factors associated with SN detection failure are skin contamination, operative position different from patient position when overlying skin is marked, differentiation of SLN from sites of lymphatic hold-up, differentiation of SLN from second-tier nodes, failure to locate SLN accurately if relying on images in one plane only, failure to locate low-count SLNs, incorrect or failure of communication of report to surgical team, and apparent non-drainage: associated with higher chance of aberrant SLN and of metastases to SLN (78). SN detection rates are not affected by tumour size or palpability (80).

Environmental Scan Results: FNRs

The current reported standard for FNR is less than 5% (78) to 5-15% (81). FNRs are not affected by tumour size or palpability (80).

Environmental Scan Results: Accuracy

There is no evidence to support or refute a training effect on accuracy (80). Accuracy is increasing by using both dyes and radioactive isotopes, which has been shown to increase SN detection rates and lower FNRs (80).

Environmental Scan Results: Recurrence

One RCT detected no difference between SLNB, SLNB→ALND, or ALND in recurrence after 46 months of follow-up (80). Long-term data were not available for review.

Environmental Scan Results: Overall Survival

One RCT detected no difference between SLNB, SLNB→ALND, or ALND in overall survival after 46 months of follow-up (80). Long-term data were not available for review.

Environmental Scan Results: Special Circumstances

DCIS

While one report states that the use of SLNB with DCIS should remain investigational (81), another report recommends it for DCIS patients with extensive, high-grade, or associated disease with a palpable mass (79), and only with total mastectomy with or without reconstruction (82).

NAC

While one report states that SLNB can be performed following primary CT (78), another notes that the use of NAC is associated with higher FNRs compared with no NAC, but not with SN detection rates (80).

Large and/or multifocal tumours

SLNB in this setting remains investigational (81) but may be considered an option for certain patients with no evidence of metastases (78).

Environmental Scan Results: Safety

Complication rates (e.g., infections, lymphedema) are significantly lower for SLNB compared with SLNB→ALND or ALND (80).

Environmental Scan Results: Training

One paper recommends that SLNB should only be performed by surgeons who have received the proper training in the technique and who have been audited for accuracy in at least 30 cases (79). Another recommends that surgeons and team should have had training followed by a period of self-audit and team audit where success is measured against the outcomes of SN detection rates and FNRs (81).

Environmental Scan Results: Auditing

Patient outcomes should be audited against the current standards of SN detection and FNRs (78,81).

Environmental Scan Results: Histopathology

SLN samples should be sliced at no more than 0.2cm intervals and submitted for microscopic evaluation in their entirety (79).

CLINICAL PRACTICE QUESTIONS

Should SLNB be the recommended standard of care for women and men with proven breast cancer whose clinical presentation is suggestive of early-stage disease?

This systematic review of the literature since the 2005 ASCO guideline (1) supports the SLNB technique as the preferred method of axillary staging for women in Ontario who present with early-stage breast cancer in the absence of palpable adenopathy.

Additional Evidence 2004-2008

For diagnostic utility outcomes, the four RCTs reported high SN detection rates (95.1%, Sentinella-GIVOM to 97.2%, NSABP B-32) and acceptable FNRs (6.7%, ALMANAC). Accuracy (94.4% Sentinella-GIVOM to 97.6%, ALMANAC), and sensitivity results (83.3%, Sentinella-GIVOM to 93.3%, ALMANAC) were all acceptable. The prospective series papers obtained reported SN detection rates ranging from 77.6% (43) to 100% (47), FNRs ranging from 1.9% (10) to 25% (13), accuracy rates ranging from 67.9% (13) to 100% (60), and sensitivity ranging from 34% (45) to

100% (27,34,36). The five papers that reported on specificity all reported a value of 100% (13,45,46,49,60).

For treatment related outcomes, the single RCT (Sentinella-GIVOM) that reported on OS, RFS, and recurrence rates detected a statistically significant difference only in locoregional control in favour of ALND (p=0.007). There was no significant difference in axillary recurrences (1/345 SLNB compared with 0/352 ALND).

The Sentinella-GIVOM trial detected a statistically significant benefit favouring SLNB over ALND for lymphedema (p=0.005) and sensory loss (p=0.004). The possible benefits associated with SLNB alone cannot be expected for SLNB→ALND in the presence of SN+ (e.g., ALMANAC: length of hospital stay, p<0.05; ACOSOG Z0011: sensory loss, p<0.05; ACOSOG Z0011: infection rates, p<0.05).

How should the results of SLNB be utilized in clinical practice?
Can level I/II axillary lymph node dissection (ALND) be avoided in patients with negative findings on sentinel lymph node biopsy (SLNB)?

Original ASCO CPG Summary

The 2005 ASCO guideline supported the use of SLNB alone for women with negative pathology on the SLNB (1). The recommendations went further to suggest level I/II ALND in the setting of a failed SLNB attempt (defined by no localization of a sentinel node), or in the circumstance of palpable clinically suspicious adenopathy.

Additional Evidence 2004-2008

The additional evidence reviewed continues to support the original summary. Full ALND can be avoided when SNs are negative on pathologic examination, as evidenced by the Sentinella-GIVOM trial where no statistically significant difference was detected between the SLNB and the ALND group in OS or RFS at 55.6 months.

Updated Summary 2008

The SLNB Expert Panel recommends that SLNB should be the preferred method of axillary staging for all persons, both male and female, with a clinical presentation of early-stage breast cancer in the absence of clinically or pathologically positive lymph nodes. Specifically, when the results of SLNB are negative:

- Patients with a negative SLNB do not require level I/II axillary lymph node dissection (ALND).
- Level I/II ALND is recommended in the setting of a failed SLNB attempt (failure is defined as no localization of a sentinel node) or in the circumstance of clinically suspicious adenopathy.

The Expert Panel supports needle biopsy of suspicious adenopathy and proceeding to ALND when the biopsy is positive.

Is level I/II ALND necessary for all patients with positive findings on SLNB?
Original ASCO CPG Summary

The original ASCO guideline (1) supported completion dissection for patients with node-positive disease, suggesting that up to 50% of patients with macrometastases and 25-35% of patients with micrometastases (0.2mm to 2mm) will have residual disease in their axilla. At that time, their conclusion was based on a determination that there was insufficient data to make a recommendation for isolated tumour cells (<0.2mm) found at SLNB.

Additional Evidence 2004-2008

While the design of the ACOSOG Z0011 trial could answer this question, as the patient population was comprised of all SN+ patients allocated to either ALND+RTorCT compared with RTorCT alone, no data on treatment-related outcomes were provided. Therefore, the Expert Panel continues to support full Level I/II ALND for patients that are SN+, based on the findings of the ASCO guideline (1). For specific patients subgroups, see the updated summary below.

Updated Summary 2008

The SLNB Expert Panel concluded that completion ALND be performed for women with positive sentinel node findings but recognized that, for some patients at high risk of complication from additional surgery (i.e., elderly or patients with significant co-morbidities), it may be reasonable to omit this step. This would be particularly true if the patient's pathological characteristics suggested a low probability of remaining disease, and their medical and radiotherapy management were unlikely to be altered if a completion ALND demonstrated additional nodal involvement.

The role of radiotherapy to control SLNB-positive patients without completion dissection is being addressed in two ongoing trials: a randomized study of complete axillary lymph node dissection versus axillary radiotherapy in sentinel lymph node-positive women with operable invasive breast cancer trial 10981 and the After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trial conducted by the European Organization for Research and Treatment of Cancer (EORTC).

Based on the SLNB Expert Panel consensus and the systematic review of the evidence, patients with positive findings on SLNB should undergo a level I/II (ALND), except in the following situations:

- For individuals with life-limiting co-morbidity, high perioperative risk, and low risk of residual disease, the decision not to perform a level I/II ALND should be made on a case-by-case basis and ideally in the context of a multidisciplinary case conference.
- High or low risk of residual axillary disease is indicated by several risk factors which include: size of primary tumour, size of metastases, absence or presence of extra-nodal extension, lymph vascular invasion, ratio of positive to negative sentinel nodes, and total number of nodes assessed. (Online decision aids are available for use that may help in these cases include the Memorial Sloan-Kettering nomogram, available at: http://www.mskcc.org/mskcc/applications/nomograms_v2/Disclaimer_Breast.aspx?type=BREAST [January 9, 2009]).
- Based on the SLNB Expert Panel opinion, preoperative needle biopsy is recommended for suspicious nodes. Patients with a biopsy confirming metastatic disease should proceed to ALND.

What is the role of SLNB in special circumstances in clinical practice? (special circumstances include large and locally advanced invasive tumours, multicentric tumours, inflammatory breast cancer, ductal carcinoma in situ (DCIS), older age (65 years or more), obesity, male breast cancer, pregnancy, evaluation of the internal mammary nodes, presence of suspicious palpable axillary nodes, prior breast or axillary surgery, and preoperative systemic therapy).

Original ASCO Guideline Summary

Special circumstances were defined in the 2005 ASCO guideline (1) as the following: large and locally invasive breast cancers (T3 or T4), inflammatory breast cancer, multicentric tumours, ductal carcinoma in situ (DCIS), older age and obesity, male breast cancer, pregnancy, evaluation of internal mammary lymph nodes, prior breast or axillary surgery, suspicious palpable axillary lymph nodes, and preoperative systemic therapy. The guideline

emphasizes that the data informing many of these special circumstances are limited. For purposes of this review, male breast cancer is not defined as a special clinical circumstance.

Additional Evidence 2004-2008

The ALMANAC trial found multifocal disease to be associated with higher FNRs. Both DCIS (38) and neoadjuvant chemotherapy (43) are associated with low SN detection rates in non-randomized studies.

There are concerns about the safety of blue dye in pregnant patients, and there are limited data describing its use. Investigational studies suggest fetal radiation exposures with non-iodine radioisotopes in the dosages used for the sentinel node technique are acceptable. Additional information and resources can be found on most nuclear medicine society websites (e.g., The British Nuclear Medicine Society (available at: http://www.bnmsonline.co.uk) [accessed January 9, 2009] (go to "Guidelines and procedures", "Other guidelines", Section 7 of "Notes for the guidance of the clinical administration of radiopharmaceuticals"); The European Association of Nuclear Medicine (available at: https://www.eanm.org/scientific_info/guidelines/gl_onco_sent_node.pdf) [accessed January 13, 2009]). Most Expert Panel members would use the SLNB technique in a pregnant woman beyond the 1st trimester, weighing risk versus benefit on a case-by-case basis in consultation with a nuclear medicine specialist.

None of the other special circumstances were reported to have significant effects on outcomes.

Updated Summary 2008

In general, the SLNB Expert Panel recommends that the specific decision to use SLNB in any special circumstance should be individualized for each patient. It is important to note that while obesity and older age does not prevent an attempt for SLNB, both circumstances are a risk factor for failed SLN mapping.

What factors affect the success of SLNB (including low rates of complications and false-negative results)?

Original ASCO CPG Summary

The 2005 ASCO Guideline (1) emphasized the proportion of patients successfully mapped as predictive of FNRs. That guideline also stated that training and case volumes are factors that influence success and highlighted the need for defined protocols and methodology for all steps of a SLNB, including pathology processing and reporting.

Additional Evidence 2004-2008

The additional evidence reviewed continues to support the original summary. As evidenced by the RCT data, SN detection rates are negatively affected by a high BMI (ALMANAC) and the tumour being located other than in the upper outer quadrant (ALMANAC). FNRs are negatively affected by tumour grade (grade 3, 9.6% versus grade 2, 4.7%) (ALMANAC), the number of SNs harvested (ALMANAC), the presence of multifocal tumours (ALMANAC), and multiple axillary node involvement (Sentinella-GIVOM).

Evidence from prospective series data show SN detection rates are negatively affected by minimal surgeon training (12,52,57), extracapsular tumour involvement (28), high BMI (28,52), and increasing age (35,52,58).

Also, evidence from prospective series data show FNR are negatively affected by the presence of multifocal tumours (30,58), larger tumour size (12,28), upper outer quadrant tumour location (12), removal of a single SN (12), a single positive SN identified (12,33), use of IHC (12), and inadequate radioactive ratio (33).

Updated Summary 2008

Several factors have demonstrated association with the success of SLNB in all patients. The SLNB Expert Panel recommends team experience, case volume, and adherence to established protocols in nuclear medicine, pathology, and surgery as key determinants of success. Successful SLNB includes low rates of complications and false negative findings. Higher localization occurs with the use of periareolar injection technique and combined blue dye and radiotracer protocol, while additional factors from the evidence suggest a lower localization rate in the obese and after prior lumpectomy.

What are the potential benefits and harms associated with SLNB?

Original ASCO CPG Summary

The SLNB Expert Panel viewed reduction in morbidity as the major benefit of SLNB. The concern of potential harm from a false-negative result has been alleviated by a prospective series study demonstrating equivalent outcomes (de Mascarel et al (1992), reference 41 in original ASCO guideline) and in the NSABP B-32 trial where the SLNB arm showed an improved node detection rate (Mamounas et al (2002), reference 108 in original ASCO guideline).

The 2005 ASCO guideline (1) emphasized fewer complications (infections, sensory changes, and lymphedema) with the SLNB technique. The report clearly cautions about the potential false-negative results and mentions that there is limited data from controlled clinical trials comparing SLNB to ALND.

Additional Evidence 2004-2008

The additional evidence reviewed continues to support the original summary. For lymphedema, the ALMANAC trial did not detect a difference between ALND and SLNB, while the Sentinella-GIVOM trial did at 12 months and in favour of SLNB. For sensory loss, the ALMANAC trial did not detect a difference between ALND and SLNB, while the ACOGOG Z0011 trial detected a difference at 12 months favouring ALND when compared to SLNB→ALND ($p<0.05$), The Sentinella-GIVOM trial detected a difference at 12 months favouring SLNB ($p=0.004$). For intercostobrachial nerve division rates, the ALMANAC trial did not detect a difference between the SLNB and ALND arms. For impairment of shoulder function, neither the ALMANAC nor the Sentinella-GIVOM trial detected a difference between the groups, but the Sentinella study favoured SLND for decreased numbness, reduced pain, and better arm movement. For infection rates, the ALMANAC trial did not detect a difference between the groups, while the ACOSOG Z0011 trial detected a statistically significant difference in favour of ALND ($p<0.05$). For time to resumption of normal duties, the ALMANAC trial did not detect a difference between groups. For pain, the Sentinella-GIVOM trial no longer detected a difference between the groups at 12 months ($p=0.33$).

The prospective series paper that reported on these outcomes detected significant benefits favouring SLNB over ALND for muscle weakness, shoulder stiffness, breast area numbness, and pain, numbness, or strange sensations in an arm (all $p<0.05$) (54).

Updated Summary 2008

The SLNB Expert Panel felt the current data strongly favoured the SLNB technique, demonstrating less morbidity with equivalent positive-node detection rates in head-to-head comparisons with the ALND method.

Benefits

- Less invasive surgery (outpatient procedure and no need for drains)

- Fewer complications (i.e., infections, sensory changes and lymphedema)
- Enhanced pathologic staging

Harms
- Possible allergic reactions to blue dye
- Caution about FNRs
- No long-term survival data

TECHNICAL ASPECTS OF SLNB

- **What is the recommended mapping technique for SLNB?**

In Canada, radioisotopes must be used at a licensed nuclear medicine facility. Many institutions are performing sentinel node biopsies by partnering with a neighbouring nuclear medicine department if that service in not available in their own setting. By adjusting the timing and dose of the radioisotope injection, some patients are able to be injected the preceding day in a neighbouring community institution or centre and still have their sentinel node surgery at their local hospital.

Several isotopes are in use and vary with the nuclear medicine facility involved. Examples of radioisotopes used for sentinel node biopsies include rhenium sulphur colloid, technetium sulphur colloid, and antimony-based compounds.

Mapping techniques should be consistent within an institution to facilitate any planned audits or the interpretation of long-term results. The evidence suggests a dual injection technique with radioisotope and vital blue dye to maximize localization rates. However, some evidence from experienced groups demonstrates equivalent localization rates with a single injection protocol (1). Recent literature and current clinical practice demonstrate a high localization rate using a periareolar injection in the meridian of the tumour (34).

Lymphoscintigraphy is not mandatory, although many practitioners find a lymphoscintogram helpful (1,6,20,21). A functioning gamma probe is necessary to conduct the radioisotope technique.

There are no known harmful effects due to radiation from the low doses of radioisotope used for SLNB. Operating room staff and pathology personnel do not need to employ any special precautions when handling the tissue as described in Appendix 3 of the ASCO guideline (1), although practices do vary according to the rules of the institution involved.

- **What operative technique is recommended?**

With the radioisotope technique the incision may be guided by gamma probe readings. Surgeons identify sentinel node(s) with the probe. With the radioisotope technique, it is also possible to demonstrate that radioactive nodes have been removed by performing ex vivo counts on the resected tissue. After removing the sentinel node or nodes many surgeons demonstrate residual basin activity that is less than 10% of the hottest ex vivo count as per the NSABP B-32 protocol (6).

The ALMANAC trial data suggests there is little value in resecting more than four sentinel nodes (19). A node completely replaced by tumour may not effectively take up dye or radiotracer. For this reason, most protocols advocate removing a grossly or palpably suspicious note during the sentinel node procedure even if it has not taken up the localizing agent (6).

- **What is the recommended technique for pathological processing, handling, and reporting?**

While published protocols vary across institutions, many advocate some form of serial sectioning at no more than 2mm intervals for the evaluation of sentinel nodes. Cutting excised sentinel lymph nodes into sections no thicker than 2.0 mm parallel to the longest meridian is recommended. This allows for the recognition of small metastatic deposits that might be missed by the examination of a lymph node that has been bivalved. H/E staining is routinely employed. As recommended in Appendix 3 of the 2005 ASCO guideline (1) IHC may be used to help identify very small tumour deposits, but its use is not considered routine.

Examples of some pathology protocols can be found in Appendix 3 of the ASCO guideline (1) and in the methods section of the technical outcomes report of the NSABP B-32 randomized clinical trial (6). Reporting should be consistent with the current American Joint Commission on Cancer (AJCC) manual and should include an indication of the size of the metastatic deposits in sentinel nodes.

ORGANIZATION OF CARE QUESTIONS

The questions on the organization of care were posed by the SLNB Expert Panel to provide recommendations for the implementation of the SLNB procedure throughout Ontario. The SLNB Expert Panel identified two key areas for consideration: professional practice (experience and training) and institutional resources.

Organization of Care

1. How should the delivery of SLNB be organized in Ontario with respect to team membership, experience, and training and the institutional setting?
    a. What is the recommended experience and training for surgeons who perform SLNB?
    b. What are the recommended criteria and resources for institutions performing SLNB?

ORGANIZATION OF CARE RESULTS

How should the delivery of SLNB be organized in Ontario with respect to team membership, experience and training and the institutional setting?

What is the recommended experience and training for surgeons who perform SLNB?

It is recommended that surgeons complete at least one of the following options:

1. Training during a residency or fellowship program.
2. Mentorship with an experienced practitioner. This may include a formal didactic course.
3. Combining the procedure with a number of completion dissections to demonstrate acceptable accuracy. This option may include a formal didactic course as well.

The case volume required to reliably perform a sentinel node biopsy likely varies with individual experience and comfort with axillary surgery. The prospective series that reported this outcome suggests that high localization rates correlate with low false-negative results (40).

Many surgical residents and fellows are graduating with SLNB training. Practicing surgeons are learning the sentinel node technique through continuing professional development (CPD) programs and mentorship, and in some instances, by coupling the sentinel node technique with a completion axillary dissection to assess their own reliability before performing the procedure as a standalone operation. Both the Canadian Association of

General Surgery (http://www.cags-accg.ca/) and the American College of Surgeons (77) have policy statements on the acquisition of new surgical skills outside a residency program.

In the current literature, there were varying degrees of required training, in particular around the number of surgeries required for competency. For example, the Education and Training Committee of the European Society of Surgical Oncology (ESSO), in their core curriculum for the specialist training in surgical oncology within Europe, suggest a minimum of 30 surgeries for SLNB, as does the Health Information and Quality Authority (79). A report on the training regimen for the NSABP B-32 trial is also available (83).

What are the recommended criteria and resources for institutions performing SLNB?

The SLNB Expert Panel recommends the monitoring of outcomes related to SLNB. Specifically, the Panel endorses the recommendations from the 2005 ASCO guideline (1), which state that surgeons:

- take a formal course on the technique, with didactic and hands-on training components
- have an experienced mentor
- keep track of individual results, including the proportion of successful mappings, FNRs, and complication rates
- maintain follow-up on all patients over time (it is important that the operating surgeon be notified of any local failures when long-term follow-up is done by others)

The Breast Section of the Royal Australasian College of Surgeons (81) in their position statement suggest the monitoring and auditing of all results related to SLNB, as does the Health Information and Quality Authority (79). Two reports recommend that patient outcomes should be audited against the current standards of SN detection and FNRs (78,81).

Clinicians and patients should have the following available:

- At minimum, access to a licensed nuclear medicine facility that follows a defined SLNB protocol to perform injections.
- A surgeon having appropriate training and experience in sentinel node detection and extraction, with access to a hand-held gamma probe, which is used to detect the SN.
- A pathologist who assesses the SLN specimens according to a standardized protocol.

These recommendations are supported by many RCTs (e.g., NSABP B-32, ALMANAC).

Overall Organization of Care Recommendation

Based on evidence gathered from an environmental scan and a systematic review the SLNB Expert Panel recommends that:

- SLNB should be performed by an experienced team to ensure equivalent results to ALND. The proportion of patients successfully mapped correlates with SN detection rates and FNRs, which are reasonable indicators of quality. Established pathology and nuclear medicine protocols need to be adhered to.
- Any axillary failures following SLNB should be documented, and the operating surgeon notified. Axillary failure may be detected by any caregiver (radiation oncologist, medical oncologist, general practitioner in oncology (GPO), primary care physicians, or nurses).

CONCLUSIONS

This systematic review of the literature published since the 2005 ASCO guideline (1) strongly supports the SLNB technique as the preferred method of axillary staging for women in Ontario who present with early-stage breast cancer with no evidence of palpable adenopathy. Experienced teams produce results equivalent to ALND. The proportion of patients successfully mapped correlates with SN detection rates and FNRs, and these are reasonable indicators of quality.

The Expert Panel acknowledges that mature RCT data reporting treatment-related outcomes were not available for review, and future updates of this document will incorporate these data when published.

ONGOING TRIALS (www.clinicaltrials.gov) (updated August 21, 2008).

Protocol ID	Title
NCT00507611	Sentinel lymph node mapping and biopsy for predicting the axillary lymph node status after completion of preoperative neoadjuvant systemic chemotherapy in patients who had biopsy-proven axillary lymph node involvement at initial presentation. Study ID: OSU-06077 Status: recruiting Last updated: July 25, 2007
NCT00572481	ARM: Axillary Reverse Mapping. Study ID: UAMS 78076 Status: recruiting Last updated: June 2, 2008
NCT00357487	Sentinel lymph node identification in case of breast cancer. Clinical evaluation of a new intra-operative probe and a mini gamma camera. Study ID: 3704 Status: closed Last updated: March 8, 2007
NCT00293865	Prospective multicentric study of sentinel lymph node assessment following previous surgical biopsy for early breast cancer. Study ID: BRD 05/11-M Status: not yet recruiting Last updated: March 9, 2007
NCT00003654	Diagnostic study of patent blue V dye to identify sentinel lymph nodes in patients with Stage I or IIA breast cancer. Study ID: CDR0000066746, FRE-FNCLCC-96008, EU-98055 Status: not yet recruiting Last updated: July 23, 2008
NCT00014612	Phase III randomized study of complete axillary lymph node dissection versus axillary radiotherapy in sentinel lymph node-positive women with operable invasive breast cancer. Study ID: CDR0000068566, EORTC-10981, EORTC-10981-AMAROS Status: recruiting Last updated: July 23, 2008
NCT00072293	Phase III randomized study of surgical resection with or without axillary lymph node dissection in women with clinically node-negative breast cancer with sentinel node micrometastases. Study ID: CDR0000339581, IBCSG-23-01, EU-20319 Status: recruiting Last updated: July 23, 2008
NCT00144898	Comparing conventional axillary dissection versus sentinel node resection in clinically node-negative operable breast cancer.

Protocol ID	Title
	Study ID: 2003.312 Status: recruiting Last updated: October 3, 2007
RACS-SNAC	Sentinel lymph node biopsy versus axillary clearance in operable breast cancer Study ID: NR Status: N/A Last updated: not listed

CONFLICT OF INTEREST

Members of the Expert Panel were asked to disclose information on potential conflicts of interest. None of the Panel identified any conflicts, and therefore, no action in response was required.

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Appendix A. SLNB Expert Panel members.

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Appendix B. AGREE scores for the 2005 ASCO Guideline.

Guideline		ASCO, 2005. (1)
Domain	**Scope and Purpose**	100%
	Stakeholder Involvement	53%
	Rigor of Development	80%
	Clarity and presentation	94%
	Applicability	35%
	Editorial Independence	94%
Overall		**76% (Strongly recommend)**
Number of Reviewers		4

Strongly recommend
The guidelines rated high (3 or 4) on the majority of items and most domain scored are above 60%. This indicates that the guideline has a high overall quality and that it could be considered for use in practice without provisos or alterations.

Recommend (with provisos or alterations)
The guidelines rated high (3 or 4) or low (1 or 2) on a similar number of items and most domains scored are between 30 or 60%. This indicates that the guideline has a moderate overall quality. This could also be due to insufficient information or a lack of information in the guideline for some of the items. If provisos or alterations are made–and sufficient information is provided on the guideline development method–the guideline could still be considered for use in practice, in particular when no other guidelines on the same clinical topic are made.

Would not recommend
The guidelines rated low (1 or 2) on the majority of items and most domain scores are below 30%. This indicates that the guideline has a low overall quality and serious shortcomings. Therefore, it should not be recommended for use in practice.

Appendix C. MEDLINE search strategy.

exp Sentinel lymph node biopsy/
axilla$.tw.
sentinel.mp.
1 and 2 and 3
exp Breast neoplasms/ or exp Breast cancer/
((breast or mammary or ductal) and (cancer or carcinoma or neoplasm$ or tumo?r)).tw.
5 or 6
4 and 7
limit 8 to yr="2004-2007"
(comment or letter or editorial or interview or lectures or news).pt.
9 not 10
Limit 11 to English language
Limit 12 to human
Remove duplicates from 13
Limit 14 to “review”
14 not 15

Appendix D. Table of procedural steps in the systematic review.

Stage	MEDLINE		NGC		Cochrane/ DARE		SABC		ASCO		Environmental scan		TOTAL
Initial search	571		1		7		124		23		-		
Ordered for full-text review	152		0		0		11		2		-		
Retained	65	+	0	+	0	+	7	+	1	+	5	=	**78**

Note: NGC, National Guidelines Clearinghouse; Cochrane, Cochrane database of systematic reviews; DARE, Database of Abstracts of Reviews of Effects; SABC, San Antonio Breast Conference proceedings; ASCO, American Society of Clinical Oncology proceedings.

Appendix E. Randomized controlled trial results.

Author Year (reference)	Study Details (comparison, exclusions, etc.)	Outcomes	
ALMANAC Trial			
Validation Phase reports			
Goyal A et al 2005 (1)	• SLNB → ALND (validation phase report) • N=823 early stage (T1-3) breast cancer patients **Exclusions:** • Multicentric cancer • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast of axilla • Pre-existing limb disease	Lymphatic mapping success	NR
		SN detection rate	98% (581/590)
		False-negative rates	7% (13/192)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Males were included in study population	
		Benefits/harms reported on:	
		NR	
Goyal A et al 2006 (2)	• SLNB → ALND (validation phase report) • N=842 early stage (T1-3) breast cancer patients **Exclusions:** • Multicentric cancer • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast of axilla • Pre-existing limb disease	Lymphatic mapping success	NR
		SN detection rate	96% (270/282)
		False-negative rates	6.7% (19/282)
		Negative predictive value	NR
		Overall accuracy of SLNB	97.6% (782/803)
		Sensitivity	93.3% (263/282)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Males were included in study population	
		Benefits/harms reported on:	
		Factors associated with mapping failure: • High BMI (p<0.001) • tumour location other than upper outer quadrant (p=0.008) • Non-visualization of SN on pre-op lymphoscintigraph (p<0.001) FN is associated with: • Tumour grade (G3 9.6% vs. G2 4.7%, p=0.022) • Number of SNs harvested (1:10.0% vs. 3+:1.1%, p=0.01)	
Randomization Phase reports			
Clarke D et al 2004 (3)	• SLNB → ALND (SN+) versus ALND (all) • N=13 surgeons • N=520 early stage (T1-3) breast cancer patients **Exclusions:** • Multicentric cancer • Previous ipsilateral breast or axillary surgery	Lymphatic mapping success	NR
		SN detection rate	96.3%
		False-negative rates	5.9% (10/170)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR

	• Previous RT to ipsilateral breast of axilla • Pre-existing limb disease	**Special circumstances reported on:**	
		Males were included in study population	
		Benefits/harms reported on:	
		NR	
		Other:	
		Results obtained do not support a learning curve for SLNB, but two issues were identified: -localization of the SN -pathologic analysis of the SN	
Goyal A et al 2004. (4)	• SLNB → ALND (SN+) versus ALND (all) • N=618 early stage (T1-3) breast cancer patients (N=4 male) **Exclusions:** • Multicentric cancer • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast of axilla • Pre-existing limb disease	Lymphatic mapping success	NR
		SN detection rate	96% (593/618)
		False-negative rates	3% (17/593)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Males were included in study population	
		Benefits/harms reported on:	
		NR	
Fleissig A et al 2006 (5)	• SLNB → ALND (SN+) (N=515) versus ALND (LII-III or 4 node) (N=516) • Total N=1031 early stage (T1-3) breast cancer patients **Exclusions:** • Multicentric cancer • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast of axilla • Pre-existing limb disease	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Males were included in study population	
		Benefits/harms reported on:	
		Main outcome in this report was Trial Outcome Index (TOI), reported on N=405 SLNB patients and N=424 ALND patients. Results detected significant benefit favouring the SLNB group at all time points (1,3,6,18 months) at $p<0.05$.	
Goyal A et al 2006 (6) [SABC Abstract]	• SLNB → ALND (SN+) (N=83) versus ALND (all) (N=373) • early stage (T1-3) breast cancer patients **Exclusions:** • Multicentric cancer • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast of axilla	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	

	• Pre-existing limb disease	Males were included in study population	
		Benefits/harms reported on:	
		No significant differences were found between the groups for: Lymphedema, sensory loss, intercostobrachial nerve division rates, impairment of shoulder function, infection rate, time to resumption of normal duties. Significant differences were found between the groups for: Median operative time to completion for two-step ALND (33 min.) versus one-step ALND (22 min.), p<0.05. Total median axillary operative time, two-step ALND (53 min.) versus one-step (22 min.), P<0.05. Hospital length of stay two-step ALND (10 d) versus one-step ALND (6d), p<0.05.	
Goyal A et al 2008 (7)	• SLNB → ALND (SN+) (N=83) versus ALND (N=96) • Total N=179 early stage (T1-3) breast cancer patients **Exclusions:** • Multicentric cancer • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast or axilla • Pre-existing limb disease	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Males were included in study population	
		Benefits/harms reported on:	
		No sig. differences reported between groups for: lymphedema, sensory loss, intercostobrachial nerve division rates, impairment of shoulder movement, infection rates, or time to resumption of normal activities post-surgery.	
Subgroup analysis: unifocal versus multifocal tumours.			
Goyal A et al 2004 (8)	• SLNB → ALND (SN+) versus ALND (all) Sub-group analysis of ALMANAC trial: 75 (of 842) patients with early stage (T1-3) breast cancer and multifocal tumours **Exclusions:** • Previous ipsilateral breast or axillary surgery • Previous RT to ipsilateral breast of axilla • Pre-existing limb disease	Lymphatic mapping success	NR
		SN detection rate	94.7%
		False-negative rates	8.8%
		Negative predictive value	92.5%
		Overall accuracy of SLNB	95.8% (68/71)
		Sensitivity	91.2%
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Males were included in study population. Multicentric versus unifocal tumours: Successful ID of SN: p=0.45 FNR: p=0.05 (favouring unifocal) Accuracy, sensitivity, NPV: all p=n.s.	
		Benefits/harms reported on:	
		NR	

ACOSOG Z0011 Trial			
Lucci A et al 2007 (9)	• SLNB → ALND (N=455) • SLNB alone (N=446) • Total N= 891 women with T1-2N0M0 breast cancer with 1 or 2 positive SNs **Exclusions:** • Previous cancer within 5 years • Bilateral breast cancer • Multicentric disease • Three or more positive SNs • Gross extracapsular invasion • Matted nodes at SLND • Contraindications to ALND • Any risk factor precluding future treatment	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Significant benefits detected for SLNB over ALND for: • Infection ($p<0.05$) • Axillary seroma ($p<0.0001$) • Axillary paresthesias ($p<0.05$)	
NSABP B-32 Trial			
Krag DN et al 2007 (10)	• SLNB → ALND (N=2807) • SLNB → ALND if SN+ (N=2804) • Total N=5611 women with invasive T1-3 breast cancer	Lymphatic mapping success	NR
		SN detection rate	97.2% (5379/5536)
		False-negative rates	9.8% (75/766)
		Negative predictive value	NR
		Overall accuracy of SLNB	97.1% (2544/2619)
		Sensitivity	90.2% (691/766)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Sentinella-GIVOM			
Del Bianco et al 2008 (11)	• SLNB → ALND if SN+ (N=336) • ALND (N=341) • Total N= 667 **Exclusions:** • Non-palpable tumours • multiple tumours • DCIS • tumours >3cm • clinically positive axilla • distant metastases • previous neoadjuvant therapy	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Significant benefits favouring SLNB detected for: • Lymphedema ($p=0.005$) • Shoulder movement restriction ($p=0.005$)	

		• Pain (p=0.006) • Numbness (p<0.0001) No difference detected in SF-36 scores	
Zavagno G et al 2008 (12)	• SLNB → ALND (N=352) • SLNB → ALND if SN+ (N=345) • Total N=749 T1-2 breast cancer patients (N=3 T4 allocated to SLNB arm) • Median 55.6 month follow-up **Exclusions:** • Non-palpable tumours • multiple tumours • DCIS • tumours >3cm • clinically positive axilla • distant metastases • previous neoadjuvant therapy	Lymphatic mapping success	NR
		SN detection rate	95.0% overall 95.1% SLNB 94.9% ALND
		False-negative rates	16.7% (18/108) ALND
		Negative predictive value	92.3% (215/233) ALND
		Overall accuracy of SLNB	94.4% (305/323) ALND
		Sensitivity	83.3% (90/108) ALND
		Specificity	100% ALND
		Recurrence rates	4.6% (16/345) SLNB vs. 0.85% (3/352) ALND (locoregional)
		Recurrence-free survival	87.6% SLNB vs. 89.9% ALND (p=ns)
		Overall survival	94.8% SLNB vs. 95.5% ALND (p=ns)
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Significant benefit favouring SLNB for: • Lymphedema (p=0.01) • Restriction of shoulder mobility (p<0.05) • Numbness (p<0.05) • PGWBI scores (anxiety & general index, p<0.05) No difference between arms detected for HRQoL or SF-36.	
Zavagno G et al 2008 (13)	• SLNB → ALND (all) (N=334) • SLNB → ALND if SN+ (N=363) • Total N=749 women with invasive primary breast cancer tumours ≤3cm and clinically negative axillas (N=697 evaluable) • Median 56 month follow-up **Exclusions:** • Non-palpable tumours • multiple tumours • DCIS • tumours >3cm • clinically positive axilla • distant metastases • previous neoadjuvant therapy	Lymphatic mapping success	NR
		SN detection rate	95% overall SLNB: 95.1% ALND: 94.9%
		False-negative rates	16.7% (18/108)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	SLNB: 0.2% (1/363) ALND: 0
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		FNR associated with multiple axillary node involvement (p=0.018)	

Note: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; N, number; T, tumour; RT, radiotherapy; NR, not reported; SN, sentinel node; BMI, body mass index; FN, false negative; SN+, positive sentinel node; L, level; N0, node negative; M, metastases; DCIS, ductal carcinoma in situ; PGWBI, Psychological General Well-Being Index; HRQoL, Health-related Quality of Life Index; SF-36, SF-36 health scale; FNR, false-negative rates.

Appendix F. Non-randomized study results (cohort, prospective series, prospective audits, case-control, and retrospective).
All False-negative rates are as reported by the authors, as data did not allow for calculation (see discussion, pg. 7)

Author Year (reference)	Study Details (comparison, exclusions, etc.)	Outcomes	
Cohort study			
Rietman JS et al 2006 (14)	• SLNB or ALND • SLNB → ALND if SN+ (N=57) • ALND (N=124) • N=204 T1-2 breast cancer patients • Median 24 month follow-up	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Significant benefit favouring SLNB for: • Upper limb function • ADL score • QoL (QLQ-C30, EORTC QLQ-BR23) All p<0.05	
Prospective series			
Litz CE et al 2004 (15)	• SLNB → ALND if SN+ • N=96 female patients	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	19.8% (19/96)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	34% (HE + cytokeratin immunostain) 40% (HE)
		Specificity	100%
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Merson M et al 2004 (16)	• SLNB → ALND if SN+ • N=371 patients with T1-2N0 breast cancer • Mean 20 month follow-up	Lymphatic mapping success	99%
		SN detection rate	NR
		False-negative rates	10.6%
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	73%
		Specificity	NR
		Recurrence rates	0.5% (2/371)
		Recurrence-free survival	NR
		Overall survival	NR

		Special circumstances reported on:	
		Male patients included in study population	
		Benefits/harms reported on:	
		NR	
Nagashima T et al 2004 (17)	• SLNB → ALND if SN+ • N=183 female patients • Median 25 month follow-up **Exclusions:** • Multiple tumours • Previous axillary surgery	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	4.1% (6/183)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		N=30 DCIS (30/183)	
		Benefits/harms reported on:	
		NR	
Schirrmeister H et al 2004 (18)	• SLNB → ALND • N=814 female breast cancer patients (Tis→T4). 4.2% T3/4	Lymphatic mapping success	NR
		SN detection rate	84% (both single and dual agent) 89.6% (dual agent alone)
		False-negative rates	8.4% (dual)
		Negative predictive value	95.7% (dual)
		Overall accuracy of SLNB	NR
		Sensitivity	91.6% (dual)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Training has a sig. effect on SN detection rates, but not on FNR.	
Agarwal T et al 2005 (19)	• SLNB → ALND (4 node sampling) • N=234 T1-3 breast cancer patients (T3 N=3) • Median 41.5 month follow-up **Exclusions:** • Multifocal breast cancer	Lymphatic mapping success	NR
		SN detection rate	94.4% (221/234)
		False-negative rates	4% (9/221)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	94.5% (13/234 SN-) 100% (221/221 SN+)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	

Asoglu O et al 2005 (20)	• SLNB → ALND • N=104 previous excisional biopsy • N=162 FNAB or core biopsy • Total N=266 patients with T1-2 breast cancer **Exclusions:** • Prior axillary dissection • Multicentric tumour • DCIS • Previous RT • Clinically positive axilla	Lymphatic mapping success	94.5%
		SN detection rate	94.3%
		False-negative rates	1.9% (3/162)
		Negative predictive value	97.1% (101/104)
		Overall accuracy of SLNB	98% (150/153)
		Sensitivity	94.2% (49/52)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Bergkvist L et al 2005 (21)	• SLNB → ALND • N=675 T1-3N0 breast cancer patients **Exclusions:** • Multicentric tumours • Previous biopsy • Breast reduction surgery • Previous CRT	Lymphatic mapping success	NR
		SN detection rate	95.5% (638/675)
		False-negative rates	7.7% (21/271) 3.5% (unifocal tumours where surgeon had at least 30 prior procedures)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Multifocal tumour is risk factor for FNR	
Gui GPH et al 2005 (22)	• SLNB → ALND (N=84) • 4 node ANB (N=81) • N=165 early breast cancer patients **Exclusions:** • Prior neoadjuvant CT • Age >75 years • DCIS • Recurrent breast cancer • Metastatic disease	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	4.5% (2/44) 7.7% (2/26) (SLNB) 0 (0/18) (4 node)
		Negative predictive value	98.4% (121/123) 96.7% (58/60) (SLNB) 94.3% (63/67) (4 node)
		Overall accuracy of SLNB	NR
		Sensitivity	95.5% (42/44) 92.3% (24/26) SLNB 100% (18/18) (4 node)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR

		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Jeruss JS et al 2005 (23)	• SLNB → ALND if SN+ • N=864 T1-4 breast cancer patients (0.5% T4) • Median 27.4 month follow-up	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	4.5% (11/244)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Kinoshita T et al 2005 (24) [SABC Abstract]	• NAC → SLNB → ALND (all) • N=77 stage 2/3 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	93.5% (72/77)
		False-negative rates	11.1% (3/27)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		All patients received neoadjuvant CT	
		Benefits/harms reported on:	
		NR	
Loussouarn D et al 2005 (25) [SABC Abstract]	• SLNB → ALND if SN+ • N=193 patients with invasive breast cancer	Lymphatic mapping success	NR
		SN detection rate	100%
		False-negative rates	NR
		Negative predictive value	75%
		Overall accuracy of SLNB	NR
		Sensitivity	64%
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		DCIS patients were included (82%)	
		Benefits/harms reported on:	
		NR	
Martin EP et al 2005 (26)	• SLNB → ALND • N=4117 T1-2N0 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	94% (3870/4117)
		False-negative rates	2.6% (106/4117)
		Negative predictive value	NR

		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Factors associated with FNR: tumour size >2.5cm, upper/outer quadrant tumour location, removal of a single SN, minimal surgical experience, a single positive axillary lymph node, use of IHC (all $p<0.05$)	
Pelosi E at al 2005 (27)	• SLNB → ALND if SN+ • N=237 T0-2 breast cancer **Exclusions:** • Palpable axillary lymph nodes • Tumour size >3cm • Multifocal or multicentric cancer	Lymphatic mapping success	NR
		SN detection rate	99.2% (244/246)
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Posther KE et al 2005 (28)	• SLNB → ALND • SLNB alone • N=5327 women with T1-2N0M0 breast cancer	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		• Failure to detect a SN associated with >BMI, >age. • Failed SLND associated with surgeon having <50 prior procedures. • The authors endorse surgeons have 25-30 consecutive SLNB→ALND with a minimum success rate of 85% and a maximum FNR of 5%.	
Ronka R et al 2005 (29)	• SLNB (N=43) or ALND (N=40) • Total N=109 T1-2N0 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR

	• Minimum 12 month follow-up	Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Significant benefits favouring SLNB over ALND for: • Muscle weakness (p=0.014) • Shoulder stiffness (p=0.047) • Pain in arm (p=0.039) • Numbness in breast area (p=0.005) • Numbness in arm (p=0.0001) • Strange sensations in arm (p=0.0001)	
Sanjuan A et al 2005 (30)	• SLNB → ALND if SN+ • Total N=427 • Median 21.2 month follow-up	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	3.45% (2/66)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Tanaka Y et al 2005 (31)	• SLNB alone (N=27) • SLNB → ALND (N=43) • Total N=70 T1-3N0-3aM0 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	90% (63/70)
		False-negative rates	5% (3.5/70)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		All patients received neoadjuvant CT	
		Benefits/harms reported on:	
		NR	
Benson JR et al 2006 (32) [SABC Abstract]	• SLNB → ALND (if SN+) • N=267 N0 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	99% (264/267)
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR

		Overall survival	NR
		Special circumstances reported on:	
		Patients with multifocal disease were included	
		Benefits/harms reported on:	
		NR	
Carcoforo P et al 2006 (33)	• SLNB → ALND (N=50) • SLNB → ALND if SN+ (N=741) • Total N=791 • Median 32.3 month follow-up	Lymphatic mapping success	87.3% (647/741)
		SN detection rate	NR
		False-negative rates	0.5% (3/566)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
de Kanter AY et al 2006 (34)	• SLNB → ALND (all) • N=138 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	3.6% (5/138)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Risk factors for FNRs: • Inadequate radioactive ratio • Inadequate excision (not all hot nodes removed, e.g. after SN removed, remaining nodes not checked)	
D'Eredita G et al 2006 (35)	1: SLNB → ALND (all) (N=115) Lymphoscintigraphy+dye 2: SLNB → ALND (all) (N=40) Blue dye alone 3: SLNB → ALND (all) (N=40) Blue dye+radioisotope	Lymphatic mapping success	NR
		SN detection rate	1: 94.8% (109/115) 2: 95% (38/40) 3: 100% (40/40)
		False-negative rates	1: 9% 2: 0% 3: 0%
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	1: 91% (30/33) 2: 100% (12/12) 3: 100%

			(11/11)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Imoto S et al 2006 (36)	• SLNB → ALND (all) • N=165 SN- breast cancer patients • Median 73 month follow-up	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	6% (10/165)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Kim HJ et al 2006 (37) [SABC Abstract]	• N= 139/942 multifocal breast cancer patients SLNB → ALND • N=803/942 unifocal breast cancer patients SLNB → ALND • N=884 patients received ALND (757/884 multifocal, 127/884 unifocal)	Lymphatic mapping success	NR
		SN detection rate	Multifocal: 97.8% (757/884) Unifocal: 98% (787/803) p=ns
		False-negative rates	Multifocal: 7.9% (3/38) Unifocal: 8.6% (15/174) p=ns
		Accuracy	Multifocal: 97.6% (124/127) Unifocal: 98% (742/757) p=ns
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Multifocal breast cancer patients included.	
		Benefits/harms reported on:	
		NR	
Knauer M et al 2006 (38)	• SLNB →ALND	Lymphatic mapping success	NR
		SN detection rate	91.5%

	• N=142 breast cancer patients (a subgroup of 3730 clinically node-negative patients) • Median 17 month follow-up		(130/142)
		False-negative rates	4% (3/75)
		Negative predictive value	93.3%
		Overall accuracy of SLNB	97.3%
		Sensitivity	96%
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		All patients had multifocal cancer or DCIS	
		Benefits/harms reported on:	
		NR	
Lo YF et al 2006 (39)	• SLNB → ALND • N=174 T1-2 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	94.3% (165/175)
		False-negative rates	6.3% (3/48)
		Negative predictive value	97.5% (117/120)
		Overall accuracy of SLNB	98.2% (162/165)
		Sensitivity	93.7% (45/48)
		Specificity	100% (48/48)
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Three patients were male.	
		Benefits/harms reported on:	
		NR	
Motomura K et al 2006 (40)	• SLNB → SN+ → Three-axillary node sampling → ALND • N=47 breast cancer patients (a subgroup of 293 consecutive patients)	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	93.1% (40/43)
		Overall accuracy of SLNB	95.3% (41/43)
		Sensitivity	87.5% (38/43)
		Specificity	100% (43/43)
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Sanguinetti A et al 2006 (41)	• SLNB → ALND (all) • N=178 early stage breast cancer patients **Exclusions:** • Previous breast surgery	Lymphatic mapping success	NR
		SN detection rate	98% (174/178)
		False-negative rates	11% (20/178)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR

		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Tan MP 2006 (42)	• SLNB → ALND or SLNB alone if SN- • N=50 T1-2 or DCIS patients SLNB → ALND results only	Lymphatic mapping success	NR
		SN detection rate	96.2% (50/52)
		False-negative rates	0
		Negative predictive value	NR
		Overall accuracy of SLNB	100% (29/29)
		Sensitivity	82% (9/11)
		Specificity	100% (20/20)
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		DCIS patients included	
		Benefits/harms reported on:	
		NR	
Bembenek A et al 2007 (43)	• SLNB → ALND (N=366) • Total N=455 consecutive breast cancer patients **Exclusions:** • Any preop treatment • Fixed, palpable mass in axilla	Lymphatic mapping success	NR
		SN detection rate	84% (380/455)
		False-negative rates	18% (24/113)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	82% (106/131)
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Failed SN detection associated with: • Extracapsular tumour involvement (p<0.0001) • BMI > 26 (p=0.003) FNR associated with tumours > 1.95 cm (p=0.039)	
Celebioglu F et al 2007 (44)	• Phase I: • SLNB → ALND (all) (N=132 patients with non-palpable breast tumours OR confirmed by diagnostic biopsy) • Phase II: • SLNB → ALND if SN+ (N=745) • Total N=877 • Median 23 month follow-up	Lymphatic mapping success	NR
		SN detection rate	Phase I: 95% Phase II: Non-palpable tumours: 95% Prior diagnostic operation: 91%
		False-negative rates	Phase I: 5.6% (1/18)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR

		Special circumstances reported on:	
		Included pts with prior diagnostic operation to ipsilateral breast or axilla	
		Benefits/harms reported on:	
		NR	
Konstantiniuk P et al 2007 (45)	• SLNB → ALND (all) (N=671) • SLNB → ALND if SN+ (N=2271) • Total N=2942 T1-4 (T3/4, 1.9%) breast cancer patients • Mean 34.4 month follow-up **Exclusions:** • Multicentric disease • Contralateral tumours • Prior neoadjuvant therapy	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	Local: ALND: 2.6% (18/671) SLNB: 0.8% (18/2271) p=0.132 Axillary: ALND: 1% (7/671) SLNB: 0.4% (8/2271) p=0.073 Distant: ALND: 5.8% (39/671) SLNB: 2.8% (64/2271) p=0.185
		Recurrence-free survival	ALND: 89.4% (71/671) SLNB: 95% (115/2271) p=0.17
		Overall survival	ALND: 94.8% (35/671) SLNB: 97.2% (64/2271) p=0.82
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Lee S et al 2007 (46)	• Preop CT →SLNB, SN+ → ALND (N=219) • No preop CT → SLNB, SN+ → ALND (N=363) • N=582 (of total N=1284) T1-4 breast cancer patients (preop CT, N=17; no preop CT, N=0)	Lymphatic mapping success	NR
		SN detection rate	Preop CT: 77.6% (170/219) No preop CT: 97% (352/363) p<0.001
		False-negative rates	Preop CT: 5.6% (7/124) No preop CT:

			7.4% (26/352) p=0.681
		Negative predictive value	Preop CT: 86.8% (46/53) No preop CT: 0
		Overall accuracy of SLNB	Preop CT: 95.9% (163/170) No preop CT: 92.6% (326/352) p=0.181
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Patients that received preop CT were included	
		Benefits/harms reported on:	
		NR	
Lelievre L et al 2007 (47)	• SLNB → ALND (all) • N=152 pT ≥ 3cm breast cancer	Lymphatic mapping success	NR
		SN detection rate	97.4% (148/152)
		False-negative rates	4% (4/99)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Procaccini E et al 2007 (48)	• N=256 T1/2 breast cancer patients, a subset of N=527 enrolled) • SLNB → ALND (if SN+) **Exclusions:** • Multicentric or multifocal disease • Clinical evidence of nodal involvement • Previous biopsy • Prior RT/CT	Lymphatic mapping success	NR
		SN detection rate	98.1% (251/256)
		False-negative rates	5.6% (14/251)
		Negative predictive value	NR
		Overall accuracy of SLNB	97.5% (250/256)
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Schule J et al	• SLNB → ALND (all)	Lymphatic mapping success	NR

2007 (49)	• N=109 women with breast cancer tumours >3cm in diameter **Exclusions:** • Neoadjuvant CT/RT • Previous breast surgery • Multifocal tumours • Clinically suspected axillary node metastases	SN detection rate	94.5% (103/109)
		False-negative rates	13% (8/64)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		SN detection rates associated with increasing age (p=0.032) FNR associated with multifocal tumours (p=0.026)	
Shen J et al 2007 (50)	• SLNB → ALND (N=61) • N=56 evaluable patients with T1-4,N0,M0 (T4, N=12) breast cancer (of N=69 total)	Lymphatic mapping success	NR
		SN detection rate	92.8% (64/69)
		False-negative rates	25% (10/40)
		Negative predictive value	61.5% (16/26)
		Positive predictive value	100% (22/22)
		Overall accuracy of SLNB	67.9% (38/56)
		Sensitivity	65.8% (22/32)
		Specificity	100% (16/16)
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Takei H et al 2007 (51)	1. SLNB SN- (N=1062) 2. SLNB → ALND (all) SN- (N=56) 3. SLNB SN+ (N=127) 4. SLNB → ALND (all) SN+ (N=459) • Total N=1653 T1-4 (T4, N=6) breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	Local failure: 1. 1.7% (18/1062) 2. 5.4% (3/56) 3. 0.8% (1/127) 4. 2.2% (10/459) Regional failure: 1. 1% (11/1062) 2. 0 3. 0 4. 3.3% (15/459) Distant failure:

			1. 2.4% (26/1062) 2. 0 3. 3.9% (5/127) 4. 6.5% (30/459)
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Gimbergues P et al 2008 (52)	• Neoadjuvant CT → SLNB → ALND (all) • Total N=129 T1-3 breast cancer patients • Median 35.6 month follow-up	Lymphatic mapping success	NR
		SN detection rate	93.8%
		False-negative rates	14.3% (8/56)
		Negative predictive value	89%
		Positive predictive value	100%
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	Systemic: 3% (4/129) Local: 1.5% (2/129) Nodal: 0.75% (1/129)
		Recurrence-free survival	91% (118/129)
		Overall survival	97% (125/129)
		Special circumstances reported on:	
		All patients received preop CT.	
		Benefits/harms reported on:	
		SN detection failure associated with age >60 (p=0.0063) FNR associated with large tumour size before preop CT (p=0.045)	
Intra M et al 2008 (53)	• SLNB → ALND if SN+ (N=11) • Total N=854 patients with DCIS breast cancer • Median 41 month follow-up	Lymphatic mapping success	NR
		SN detection rate	1.4% (12/854)
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	SN+: 25% (3/12) SN-: 0
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		All patients had DCIS	
		Benefits/harms reported on:	
		NR	
Prospective audit			
Haid A et al 2006 (54)	• SLNB (N=180)	Lymphatic mapping success	NR
		SN detection rate	100%: SLNB

	• ALND (N=118) • Total N=298 invasive breast cancer patients (T1mic-T4, T4=0 SLNB, T4=4 ALND) • Minimum 46 month follow-up **Exclusions:** • DCIS • Multicentric cancer • Primary CT		(180/180) 90%: ALND (106/118)
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	0.8% (2/237)
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Case-control			
Jinno H et al 2007 (55) [ASCO Abstract]	• Cases N=46 NAC → SLNB → ALND (all) • Control N=122 SLNB → ALND (all) • Total N=168	Lymphatic mapping success	NR
		SN detection rate	NAC: 91.3% (42/46) No NAC: 99.1% (112/113) p=0.01
		False-negative rates	NAC: 23.8% (5/46) No NAC: 5.9% (2/122) p=0.05
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Accuracy	NAC: 88.1% No NAC: 98.1% p<0.01
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Retrospective reviews			
Fournier K et al 2004 (56)	• SLNB compared with SLNB → ALND (N=147 LI/II ALND) • N=194 women with T1-3 breast cancer • Mean follow-up: 12 months	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	8% (4/52)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	

		NR	
		Benefits/harms reported on:	
		NR	
Fan YG et al 2005 (57)	• SLNB → ALND if SN+ • N=115 female patients **Exclusions:** • Prior neoadjuvant tx • Non-invasive cancers • Recurrent breast cancer • Failed lymphoscintigraphy	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	5% (2/40)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	4.1% (16/390) SLNB only: 2.9% (8/275) SLNB+ALND: 6.1% (7/114)
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Schulze T et al 2006 (58)	• SLNB alone (N=31) • SLNB → ALND (N=103) • ALND (N=66) • Total N=200 • Minimum 20 month follow-up	Lymphatic mapping success	NR
		SN detection rate	91.1%
		False-negative rates	12.1% (13/103)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	0
		Recurrence-free survival	NR
		Overall survival	100% SLNB 97% ALND (3 deaths)
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		Significant benefits favouring SLNB: Time to hospital discharge (5.8d vs. 9.5d, p<0.001) Axilla drainage removal (3.4d vs. 7.2d, p<0.001) Muscular strength (15.8% vs. 48.2%, p=0.04)	
Bauerfeind IG et al 2007 (59) [SABC Abstract]	• N=88/92 NAC → SLNB → ALND • N=4/92 NAC → failed SLNB → ALND • Total N=128 breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	96% (88/92)
		False-negative rates	16.6% (5/30)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	

		NR	
		Benefits/harms reported on:	
		NR	
Bauerfeind IG et al 2007 (60)	• SLNB → ALND if SN+ (N=214) • N=406 breast cancer patients total **Exclusions:** • DCIS • Preop CT • Previous excisional biopsy	Lymphatic mapping success	NR
		SN detection rate	93%
		False-negative rates	2.8% (3/109)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Kuijit GP et al 2007 (61)	• SLNB alone (N=880) • ALND alone (N=1681) • Total N=2561 T1-4 (T4 N=13 SLNB & N=51 ALND group) breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival (5-year)	SLNB: 89% (783/880) ALND: 85% (1429/1681) p=0.026
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Lerch L et al 2007 (62)	• SLNB → ALND (all) (N=576) • SLNB alone (N=186) • Total N=765 Tis-T4 (T4, N=7) breast cancer patients	Lymphatic mapping success	NR
		SN detection rate	94.3% (175/186)
		False-negative rates	5.3% (12/186)
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Park J et al 2007 (63)	• SLNB → SN+ no ALND (N=287) • SLNB → SN+ ALND (N=1673)	Lymphatic mapping success	NR
		SN detection rate	NR
		False-negative rates	NR

	• Total N=1960 Tx-T3 SN+ breast cancer patients • Median 23 month follow-up SLNB group, 30 months ALND group	Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	Axillary recurrence: SLNB: 2% (6/287) ALND: 0.4% (6/1673) p=0.004
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Soler C et al 2007 (64) [SABC Abstract]	• SLNB only (if SN-) • SLNB → ALND (if SN+) • N=664 breast cancer patients • Mean 41 month follow-up	Lymphatic mapping success	NR
		SN detection rate	98.9% (657/664)
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	SLNB only: 0 SLNB → ALND: 1% (2/217)
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		NR	
		Benefits/harms reported on:	
		NR	
Soran A et al 2007 (65)	• SLNB -> ALND if SN+ • N=1500 breast cancer patients **Exclusions:** • Previous breast surgery • Previous axilla dissection • Clinical evidence of axillary lymph node metastases • Preop CT/RT	Lymphatic mapping success	NR
		SN detection rate	91% (1366/1500)
		False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		Patients with DCIS (N=66.8%), multifocal tumours (10.5%) included	
		Benefits/harms reported on:	
		NR	
Dominguez FJ et al 2008 (66)	• SLNB → ALND if SN+ • N=179 DCIS (T1mis-T1c)	Lymphatic mapping success	NR
		SN detection rate	98.8% (177/179)

	breast cancer patients who underwent mastectomy with SLNB (N=16 patients showed SN+ and received ALND) **Exclusions:** • DCIS with invasion or microinvasion on postmastectomy pathology review	False-negative rates	NR
		Negative predictive value	NR
		Overall accuracy of SLNB	NR
		Sensitivity	NR
		Specificity	NR
		Recurrence rates	NR
		Recurrence-free survival	NR
		Overall survival	NR
		Special circumstances reported on:	
		All patients had DCIS	
		Benefits/harms reported on:	
		NR	

Note: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; NR, not reported; T, tumour; N, node; DCIS, ductal carcinoma *in situ*; ICis, intraductal component in situ; tx, treatment; N, number; ADL, activities of daily living; QoL, quality of life; QLQ-C30, Quality of Life Questionnaire C-30; EORTC QLQ-BR23, European Organization for the Research & Treatment of Cancer's 23-item Breast Cancer Specific Quality of Life Quality of Life Questionnaire; NAC, neoadjuvant chemotherapy; HE, hematoxylin & eosin stain; SN, sentinel node; +, positive; Tis, tumour *in situ*; FNR, false-negative rates; FNAB, fine needle aspiration biopsy; RT, radiotherapy; CRT, chemoradiotherapy; -, negative; BMI, body mass index; CT, chemotherapy.

Evidence-based Series 17-5: Section 3

Sentinel Lymph Node Biopsy in Early-stage Breast Cancer: EBS Development Methods and External Review Process

R. George, M.L. Quan, D. McCready, R.B. Rumble, R. McLeod, and the Expert Panel on SLNB in Breast Cancer

A Quality Initiative of Cancer Care Ontario's Surgical Oncology Program (SOP) and Cancer Care Ontario's Program in Evidence-Based Care (PEBC)

Report Date: July 14, 2009

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed in collaboration between Cancer Care Ontario's Surgical Oncology Program (SOP) and Cancer Care Ontario's PEBC. The series is a convenient and up-to-date source of the best available evidence on the use of SNLB in early-stage breast cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

- Issues surrounding the fact that the technology has largely been adopted internationally, predicated on the assumption that equivalence or benefit in diagnostic utility and/or treatment-related outcomes has been established and despite the fact that mature trial data are unavailable in some cases.
- Issues relating to the challenges in evaluating a topic where each set of recommendations are only relevant if testing of the predicating component shows equivalence and/or benefit, e.g. discussion of treatment-related recommendations are only relevant if the diagnostic utility has been clearly established, and health-services recommendations are only relevant if treatment-related outcomes have been clearly established.
- Issues relating to the structure of the included trials: some trials included a single-arm training phase as well as the results from the randomized phase, which created multiple publications; the initial publications reported on diagnostic outcomes and later publications provided treatment-related outcomes. Also, as per protocol, ALND was offered to patients randomized into the SLNB arm when positive SLNs were detected on SLNB, which appeared to be contamination.

External Review by Ontario Clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Expert Panel on SLNB in Breast Cancer circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Expert Panel on SLNB in Breast Cancer.

BOX 1: DRAFT RECOMMENDATIONS (distributed for external review March 19, 2009)

(***Recommendations*** *appear in shaded boxes,* ***Evidence*** *appears in unshaded boxes).*

SLNB is recommended as the preferred method of axillary staging for all patients with a clinical presentation of early-stage breast cancer in the absence of clinically or pathologically positive lymph nodes

Evidence

Four randomized controlled trials (RCTs) reported high sentinel node (SN) detection rates (95.1%, Sentinella-GIVOM (3,4) to 97.2%, NSABP B-32 (5) and accuracy (94.4% Sentinella-GIVOM (3) to 97.6%, ALMANAC (6)). False-negative rates were low (e.g., 6.7%, ALMANAC (6)) with the exception of one RCT that had no training component or requirement for use of the blue dye (16.7%, Sentinella-GIVOM (3,4,7)). Node-positive rates were similar in all cases between ALND and any SLNB-alone arms. In the Sentinella-GIVOM non-inferiority trial (3,4,7)) there was only one axillary recurrence in 345 SN- patients at 55.6 months of follow-up, and similar disease-free and overall survival rates. (see Section Two for summaries of the RCTs and the prospective series data).

ALND (Level I/II) is recommended for:

- Positive results on SLNB (see *Qualifying Statement*)
- Failed SLNB attempts (failure is defined as no localization of a sentinel node)
- Positive results from a needle biopsy of clinically suspicious adenopathy

Evidence

The Expert Panel continues to support full Level I/II ALND for patients that are SN+ based on the updated review and the findings of the ASCO Guideline (8). While the ACOSOG Z0011 trial (9) includes an arm of SN+ patients treated without a completion ALND, no data on treatment-related outcomes were available at the time of this review.

Qualifying Statement

While ALND (Level I/II) is recommended for patients with positive findings on SLNB, exceptions might include:

- Individuals with life-shortening co-morbidities, high peri-operative risk, and low risk of residual disease. The decision not to perform Level I/II ALND should be made on a case-by-case basis and ideally in the context of a multidisciplinary case conference.
- High or low risk of residual axillary disease is indicated by several factors which include: size of primary tumour, size of metastases, absence or presence of extra-nodal extension, lympho-vascular invasion, ratio of positive to negative sentinel nodes, and total number of nodes assessed. (Online decision aids are available for use that may help in these cases, e.g., the Memorial Sloan-Kettering nomogram, which is available at: http://www.mskcc.org/mskcc/applications/nomograms_v2/Disclaimer_Breast.aspx?type=BREAST [January 9, 2009])

Evidence

This recommendation is based on the opinion of the Expert Panel.

ALND (Level I/II) is not recommended when the results of SLNB are negative

Evidence

Full ALND can be avoided when SNs are negative on pathologic examination as evidenced by the Sentinella-GIVOM trial (3,4,7), where no statistically significant difference was detected between the SLNB and the ALND group in OS or RFS at 55.6 months

Preoperative needle biopsy can be performed for clinically suspicious nodes. Patients with a biopsy confirming metastatic disease would proceed directly to ALND, thus avoiding SLNB.

Evidence

This recommendation is based on the opinion of the Expert Panel.

The Role of SLNB in Specific Clinical Circumstances

In general, the SLNB Expert Panel recommends the use (or not) of SLNB in each of the following clinical circumstances, noting that the decision to use SLNB in these circumstances should be individualized for each patient.

Clinical circumstances recommended for SLNB

- T1 or T2 tumours
- Multicentric tumours
- DCIS (with mastectomy)
- Older age*
- Obesity*
- Bilateral breast cancer

Evidence

The majority of patients in the four RCTs reviewed were T1/2, although this was not consistent throughout the trials. The use of SLNB in DCIS with mastectomy is supported by a Standards document (10) and an online Clinical Practice Guideline (11). The recommendations for the use of SLNB with multicentric tumours, older age, obesity, and bilateral breast cancer were based on Expert Panel consensus, a subset analysis from the ALMANAC trial, and results of prospective and cohort series. (see Section 2, pages 19 and 20).

*While SLNB is recommended for both older age and/or obesity, clinicians and patients should be aware that both are risk factors for failed SLN mapping.

Clinical circumstances not recommended for SLNB

- Inflammatory T4 breast cancer
- Prior axillary surgery*

Evidence

All of the four RCTs reviewed excluded patients with inflammatory breast cancer by not including T4 lesions; the Expert Panel agrees these patients should not be considered candidates for SLNB.

*Two of the RCTs reviewed (ALMANAC (6,12-18) and ACOSOG Z0011 (9)) specifically excluded patients with prior axillary surgery. The Expert Panel agrees that these are not appropriate patients for SLNB, but would consider a patient eligible if the previous axillary surgery was a minor operation unlikely to interfere with lymphatic mapping.

Clinical circumstances with inconclusive or inadequate evidence

- Internal mammary lymph nodes*
- Before preoperative therapy*
- T3 or T4 tumours*
- DCIS (without mastectomy)*
- Suspicious palpable axillary nodes*
- After preoperative systemic therapy*
- Prior diagnostic or excisional breast surgery*
- Prior non-oncologic breast surgery*
- Pregnancy**

Evidence

There is insufficient evidence to support or refute the use of SLNB in these settings. The Expert Panel will review new evidence as it becomes available.

* For all of these circumstances, treatment decisions must be made on a case-by-case basis.

** For pregnant patients, there exist concerns about the safety of blue dye, and only small case-series describe its use. Investigational studies suggest acceptable fetal radiation exposures with non-iodine radioisotopes in the dosages used for the sentinel node technique. Additional information and resources can be found on most nuclear medicine speciality society web sites (e.g., The British Nuclear Medicine Society (available at: http://www.bnmsonline.co.uk) [accessed January 9, 2009] (go to "Guidelines and procedures", "Other guidelines", Section 7 of "Notes for the guidance of the clinical administration of radiopharmaceuticals"); The European Association of Nuclear Medicine (available at: https://www.eanm.org/scientific_info/guidelines/gl_onco_sent_node.pdf) [accessed January 13, 2009]). Individual cases must

be reviewed with a nuclear medicine specialist. Most Expert Panel members would use the SLNB technique in a pregnant woman beyond the 1st trimester, weighing risk versus benefit on a case-by-case basis.

Factors that affect the success of SLNB

Several factors are associated with successful SLNB (defined as low complication and false-negative rates [FNRs]) in all patients.

The SLNB Expert Panel acknowledges that success (defined as low complication and FNRs) is dependent on team experience, case volume, and adherence to established protocols in nuclear medicine, pathology, and surgery and recommends these factors as quality indicators.

Evidence

Evidence from prospective series data show SN detection rates are negatively affected by minimal surgeon training (19-21).

Surgeon experience was found to have a significant effect on SN detection rates (21). A Standards Document recommends that SLNB should only be performed by surgeons that have had proper training in the techniques and that have been audited for performance (10).

Two online Clinical Practice Guidelines stated that SLNB requires a multi-disciplinary team and that its success depends on the strengths of the individual components (11,22).

The SLNB Expert Panel recommends the use of periareolar injection technique and combined blue dye and radiotracer protocol (see *Qualifying Statement*).

Evidence

The majority of study protocols incorporated the dual injection technique, as stated in the original ASCO guideline (8), and the Expert Panel continues to endorse this recommendation. High localization rates are obtained when using a periareolar injection in the meridian of the tumour (23).

Qualifying Statement

The evidence suggests lower localization rates in the obese and in patients that have had a prior lumpectomy

Evidence

One RCT (ALMANAC (6,12-18)) demonstrated that SN detection rates are negatively affected by a high body-mass index (BMI), and the NSABP B-32 trial (5) showed higher FNRs after prior excisional biopsy versus needle biopsy.

Potential Harms and Benefits

Reduced morbidity is the major benefit of SLNB. The panel strongly favours the SLNB technique, which demonstrates less morbidity with equivalent positive node detection rates, compared with ALND.

Benefits

- Less invasive surgery (outpatient procedure and no need for drains)
- Fewer complications (e.g., sensory changes and lymphedema)
- Enhanced pathologic staging

Evidence

The Sentinella-GIVOM (3) trial detected a difference between ALND and SLNB for lymphedema at 12 months in favour of SLNB, and shorter-term benefits in numbness, pain, and arm movement (3,7)). For impairment of shoulder function, neither the ALMANAC (6,12-18) nor the Sentinella-GIVOM trial (3,7)) detected a long-term difference between the groups. For infection rates, the ALMANAC trial did not detect a difference between the groups. A prospective series that reported on these outcomes detected significant benefits favouring SLNB over ALND for muscle weakness, shoulder stiffness, pain in arm, numbness in breast area, numbness in arm, and strange sensations in arm (all $p<0.05$) (24).

Harms

- Possible allergic reactions to blue dye
- Caution of FNRs
- No long-term survival data

Evidence

In the RCT evidence reviewed FNRs ranged from 6.7% (ALMANAC (6)) to 16.7% (Sentinella-GIVOM (3,4)), and in the prospective series reviewed ranged from 1.9% (25) to 25% (26). The Expert Panel notes that adequate training and technique are required to achieve low FNRs.

Technical Aspects SLNB

A. Mapping Technique The recommended mapping technique is the dual injection technique with radioisotope and vital blue dye to maximize localization rates.
Evidence The majority of study protocols incorporated the dual injection technique, as stated in the original ASCO guideline (8), and the Expert Panel continues to endorse this recommendation. High localization rates are obtained when using a periareolar injection in the meridian of the tumour (23).
B. Operative Technique The Expert Panel recommends using both radioisotope and blue dye for sentinel lymph node mapping. Using this technique, the incision may be guided by gamma probe readings, allowing the surgeon to identify the sentinel node/s with the probe as well as visually to inspect for blue stained nodes and palpate for clinically suspicious nodes. With the use of the radioisotope, it is also possible to demonstrate that radioactive nodes have been removed by performing ex vivo counts on the resected tissue.
Evidence This recommendation is based on Expert Panel consensus and is supported by the NSABP B-32 trial protocol (5).
C. Pathology The recommended pathology technique is that excised sentinel lymph nodes be cut into sections no thicker than 2.0 mm parallel to the longest meridian. This allows for the recognition of small metastatic deposits that might be missed by the examination of a lymph node that has been bivalved. Hematoxylin & Eosin (H/E) staining is routinely employed. While published protocols vary across institutions, all advocate some form of serial sectioning for the evaluation of sentinel nodes.
Evidence The Expert Panel continues to support the recommendation in Appendix 3 of the 2005 ASCO Guideline (8). Immunohistochemistry (IHC) may be used to help identify very small tumour deposits, but its use is not considered routine.

ORGANIZATION OF CARE RECOMMENDATIONS

Team Recommendation SLNB should be performed by an experienced team to ensure equivalent results to ALND. The proportion of patients successfully mapped correlates with false-negative rates and is a reasonable indicator of quality. Consistent pathology and nuclear medicine protocols need to be adhered to.
Evidence: Patient outcomes should be audited against the current standards of SN detection and FNRs (22,27)). Two online Clinical Practice Guidelines state that SLNB requires a multi-disciplinary team (see INTENDED USERS, Section One) and its success depends on the strengths of the individual components. (11,22)). The Expert Panel also endorses these recommendations.
Surgeon Training Recommendation The surgeon training recommendation is completion of at least one of the following options for surgeons who perform SLNB: 1. Training during a residency or fellowship program. 2. Mentorship with an experienced surgeon (may include a formal didactic course). 3. Combining the procedure with a number of completion dissections to demonstrate acceptable accuracy (may include a formal didactic course). The SLNB Expert Panel acknowledges that the training will be different for those surgeons involved with an experienced team versus those with little to no experience.
Evidence: A Standards Document (10) and a Position Paper (27) supported this recommendation, one recommending that SLNB should only be performed by surgeons who have received the proper training in the technique and that have been audited for accuracy (10), and the other recommending that

surgeons and team should have taken training followed by a period of self and team audit where success is measured against the outcomes of SN detection rates and FNRs (27). The Expert Panel also endorses these recommendations.

System Recommendations

The minimum system recommendations are that clinicians and patients should have access to:

- a licensed nuclear medicine facility that follows a defined SLNB protocol to perform injection
- a surgeon with appropriate training and experience in sentinel node detection and extraction.
- this surgeon requires access to a hand-held gamma probe, which is used to detect the SN.
- a pathologist who assesses the SLN specimens according to a standardized protocol (for examples, see Appendix 3 of the ASCO guideline (8) and the methods section of the NSABP B-32 trial report (5).

Evidence:

These recommendations are supported by the Team and Surgeon Training evidence as well as the protocols of several RCTs (ALMANAC, NSABP B-32). The Expert Panel also endorses these recommendations.

Methods

Targeted Peer Review: During the guideline development process, eight targeted peer reviewers from Ontario who were considered clinical and/or methodological experts on the topic were identified by the Expert Panel on SLNB in Breast Cancer. This group was comprised of four surgeons, one nuclear medicine specialist, one pathologist, and two radiation oncologists. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. All nominees agreed to participate, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on March 19, 2009. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The targeted peer review period ended on April 28, 2009. The Expert Panel on SLNB in Breast Cancer reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on April 1, 2009. The consultation period ended on April 28, 2009. The Expert Panel on SLNB in Breast Cancer reviewed the results of the survey.

Results

Targeted Peer Review: Six responses were received from eight reviewers (75% response rate). Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (N=6)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.			1	2	3
2. Rate the guideline presentation.				4	2
3. Rate the guideline recommendations.			1	2	3
4. Rate the completeness of reporting.			1	1	4
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	4
6. Rate the overall quality of the guideline report.				4	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	2	4
8. I would recommend this guideline for use in practice.			1	1	4

9. What are the barriers or enablers to the implementation of this guideline report?

The following items were listed as being potential barriers according to the perceptions of the respondents of the targeted peer review: lack of resources (e.g., gamma probes, nuclear medicine capability), training (surgeons/pathologists/nuclear medicine), issues related to practice in smaller centers, absence of standardized protocols, and lack of evidence-supported guidance for the pathologic handling of SN (which will become available upon completion of the NSAPB B32 trial).

Summary of Written Comments

The Working Group reviewed the feedback obtained from the targeted peer review and determined that none warranted any change, and for this reason no responses are detailed.

Professional Consultation: Five responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Number (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				2 (40)	3 (60)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.					4 (100)
3. I would recommend this guideline for use in practice.					5 (100)

4. What are the barriers or enablers to the implementation of this guideline report?

The following items were listed as being potential barriers according to the perceptions of the respondents of the professional consultation: nuclear medicine capability, single tracer isotope licensing with federal nuclear regulators, and regional training and financial support for training (surgeons/pathologists/nuclear medicine).

The following items were listed as being potential enablers according to the perceptions of the respondents of the professional consultation: patient demand/preference for SLNB and the evidence in support of SLNB.

Summary of Written Comments

The main points contained in the written comments were:

- In my community, there have been few barriers to the SLNB program, and putting this guideline into practice would be seamless.

Modifications/Actions

The Working Group reviewed the responses obtained from the professional consultation, and determined that the responses warranted only minor changes of an editorial nature to the recommendations and the evidence summary; for this reason, none of the responses are detailed.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Expert Panel on SLNB in Breast Cancer and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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