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The steering committee is part of Health Canada's Canadian Breast Cancer Initiative. A list of the committee members appears at the end of the article.

A patient version of these guidelines appears in Appendix 1.

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Clinical practice guidelines for the care and treatment of breast cancer:

13. Sentinel lymph node biopsy

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Guidelines for the Care and Treatment of Breast Cancer

Abstract

Objective: To provide information and recommendations to women with breast cancer and their physicians regarding what is now known about sentinel lymph node (SLN) biopsy.

Options: Axillary dissection; SLN biopsy followed by backup axillary dissection; SLN biopsy.

Outcomes: Accurate determination of cancer stage, resulting in better-informed therapeutic decisions.

Evidence: Systematic review of English-language literature published from January 1991 to December 2000 retrieved primarily from MEDLINE and CANCELIT.

Recommendations:

- Axillary dissection is the standard of care for the surgical staging of operable breast cancer.
- If a patient requests or is offered SLN biopsy, the benefits and risks as well as what is and is not known about the procedure should be outlined.
- Patients should be informed of the number of SLN biopsies performed by the surgeon and the surgeon's success rate with the procedure, as determined by the identification of the SLN and the false-negative rate (the presence of tumour cells in the axillary nodes when the SLN biopsy result is negative).
- Before surgeons replace axillary dissection by SLN biopsy as the staging procedure at their institution, they should (a) familiarize themselves with the literature on the topic and the techniques needed to perform the procedure, (b) follow a defined protocol for all 3 aspects of the procedure (nuclear medicine, surgery, pathology) and (c) perform backup axillary dissection until an acceptable success rate (as determined by the identification of the SLN and the false-negative rate) is achieved.
- A surgeon who performs breast cancer surgery infrequently should not perform SLN biopsy.
- A positive SLN biopsy result or failure to identify an SLN should prompt full axillary dissection.
- SLN biopsy is contraindicated in women who have clinically palpable nodes, locally advanced breast cancer, multifocal tumours, previous breast surgery or previous irradiation of the breast.
- Staining of tissue sections with hematoxylin and eosin, and not immunohistochemical analysis for cytokeratin, should determine adjuvant therapy.
- Participation in randomized clinical trials is encouraged.

[A patient version of these guidelines appears in Appendix 1.]

Validation: Internal validation within the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer; no external validation.

Sponsor: The steering committee was convened by Health Canada.

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Over the past several years, the technique of sentinel lymph node (SLN) biopsy has been introduced as an alternative to axillary dissection for operable breast cancer. Like laparoscopic surgery in the late 1980s, SLN biopsy is a promising new medical technique that is gaining popularity before the medical community has had time to provide adequate training and put the procedure into practice in a safe and organized manner.

In many of the clinical practice guidelines previously produced by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, results from randomized trials (level I and II evidence) were available to support the use of the therapy in question.¹ Such evidence is not yet available for the performance of SLN biopsy without axillary dissection. Although randomized trials evaluating SLN biopsy are underway, it will likely be a number of years before the results will be available.

The steering committee feels that women with breast cancer and their physicians should know more about SLN biopsy and the unanswered questions related to its performance. Women with breast cancer need this information to help them make decisions about their treatment, particularly axillary dissection. SLN biopsy is widely used in the United States, and it is increasingly being used in Canada despite the lack of data from randomized trials. The steering committee felt that it would not be feasible for all surgeons interested in using this technique to participate in the current trials open to recruitment. Based on these considerations the committee chose to review the current data, point out their limitations and make recommendations on how SLN biopsy may be adopted in practice. The recommendations that follow are consistent with those recently made by McCready and associates² on behalf of the Canadian Society of Surgical Oncology and by Spillane and Sachs.³

Methods

This guideline is based on a systematic review of the English-language literature published from January 1991 to December 2000 retrieved primarily from MEDLINE and CANCERLIT. Key words combined in the search were "breast neoplasms," "lymph nodes" and "sentinel." Because data from randomized controlled trials comparing outcomes from SLN biopsy alone versus axillary dissection are not currently available, a broader search strategy without limits set by methodological search criteria was used. Review articles and protocols of randomized trials underway were also examined to provide background information and secure additional references. Rules of evidence as described by Sackett⁴ were used for grading the levels of experimental studies.

Given the lack of data from randomized trials, the recommendations are based on a consensus, reached after extensive discussions within the steering committee. The initial draft was prepared by a member of the committee and was revised according to the reviews and feedback of several committee members. The document was then discussed by the entire committee at 3 meetings, in November 1999, March 2000 and September 2000, and further revisions were made. The final draft of the manuscript was approved by the committee before submission for publication.

Recommendations (including evidence and rationale)

Axillary dissection

- **Axillary dissection is the standard of care for the surgical staging of operable breast cancer.**

Knowledge of the histologic status of axillary lymph nodes is essential when treating a woman with operable breast cancer. The clinical guideline on axillary dissection published in 1998 states: "Removal and pathological examination of axillary lymph nodes should be standard procedure for patients with early, invasive cancer" and "For accurate staging and to reduce the risk of recurrence in the axilla, level 1 and level 2 nodes should be removed" (see guideline 4).⁵

The status of the axillary lymph nodes is an important prognostic factor. Axillary dissection allows accurate staging of the cancer and guides the selection of appropriate adjuvant therapy. Furthermore, it provides excellent local control of disease in the axilla. Data from recent randomized clinical trials suggest that effective local-regional control of the tumour can affect long-term survival (level I evidence).⁶⁻⁸ Axillary dissection, however, comes with recognized morbidity: wound infection, restriction of shoulder movement, arm problems (stiffness, loss of sensation), pain and lymphedema (see guideline 11).⁹

Sentinel lymph node biopsy

Lymphatic mapping with SLN biopsy is a new procedure that aims to replace total axillary node dissection as a staging procedure for operable invasive breast cancer. Radioactive material or a blue dye, or both, is injected locally in the breast tissue that surrounds the tumour or biopsy cavity. This material is then taken up by the lymphatic system, and the surgeon traces it with a handheld gamma probe, or follows the blue dye, until the first 1 or 2 nodes draining the peritumoural breast tissue are detected. The sentinel node(s) is (are) then removed and examined histologically for the presence of tumour cells.

The histologic status of the SLN is thought to represent the histologic status of the whole lymphatic basin from which it has been removed; that is, a negative SLN suggests that other nodes in the axilla are also negative, and a positive SLN suggests that additional nodes may be positive.

Benefits and challenges of SLN biopsy

- **If a patient requests or is offered SLN biopsy, the benefits and risks as well as what is and is not known about the procedure should be outlined.**
- **Patients should be informed of the number of SLN biopsies performed by the surgeon and the sur-**

geon's success rate with the procedure, as determined by the identification of the SLN and the false-positive rate (the presence of tumour cells in the axillary nodes when the SLN biopsy result is negative).

Benefits

There are several reasons for the current widespread interest in SLN biopsy. First, with the removal of only 1 or 2 lymph nodes, morbidity is substantially less than the morbidity resulting from axillary dissection.¹⁰ Second, with the increasing use of screening mammography, smaller tumours are being detected, and these are less likely to be associated with axillary metastases.¹¹ In such circumstances, patients receive no proven benefit from axillary dissection in the absence of positive nodes, yet they are still left with its associated morbidity. Third, staging by SLN biopsy may be more accurate: because only 1 or 2 nodes are removed, more sections per node can be made and studied by the pathologist than can routinely be examined from the whole axillary dissection specimen. Immunohistochemical studies can be performed on the SLN that would be too impractical and expensive to do on the many nodes removed by axillary dissection; however, this potential benefit remains unproven because the significance of immunohistochemical studies has yet to be determined.

Challenges

Although the concept of SLN biopsy is simple, the performance of the procedure to accurately locate, harvest and analyze the SLN in breast cancer is complex and challenging. It requires a team of members from nuclear medicine, surgery and pathology, and is only mastered after a substantial learning period.

Surgical volume appears to be an important factor in the success rate of identifying the SLN. Giuliano and colleagues^{12,13} reported that the SLN was identified in 52% of their first case series of 124, in 70% of their second case series of 50 and in 94% of their third case series of 100. In their last 160 cases, there was only 1 failure. In a study by Morrow and associates,¹⁴ the likelihood of finding the SLN was 73% in the first 10 cases performed by a surgeon and 91% after 30 cases. And finally, Cox and collaborators¹⁵ reported that surgeons performing 1 to 2 SLN biopsies per month had a success rate of 82%, those performing 3 to 6 per month had a success rate of 90%, and surgeons performing more than 6 per month had a 97% success rate.

A literature search from January 1991 to December 2000 for studies in which both SLN biopsy and axillary dissection were performed identified 53 studies, involving a total of 9303 patients.^{12,14,16-66} There were no randomized trials. The studies were all case series, some prospective and some retrospective (level IV and V evidence). In all of these studies patients first had SLN biopsy and then axil-

lary dissection. In the analyses of these studies the SLN was considered the "diagnostic test" and the status of the lymph nodes (i.e., the presence or absence of disease) the "gold standard." It is of interest that a positive SLN was always counted as both a positive test result and a positive gold standard. Hence the positive predictive value and specificity were always 100% (i.e., there were never any false-positive results). In one study, the SLN was the only positive node in 9% of cases,²⁵ whereas in another study it was the only positive node in as many as 77% of cases.⁶³ Because the results of the SLN biopsy are used to decide on adjuvant therapy, the false-negative rate should be as near to 0 as possible. The false-negative rate, calculated as the number of cases in which the biopsy result was negative divided by the total number of patients in whom the axillary status was positive, ranged from 0% to 22.2%.

The potential effect of SLN biopsy on local disease control in the axilla and on overall patient survival needs to be considered. It has been reported that, without axillary dissection, the recurrence rate in the axilla is as high as 28% after a 10-year follow-up.⁵ Although SLN biopsy is not the equivalent of no treatment of the axilla (as positive cases are generally submitted to axillary dissection) there are no data on long-term local recurrence rates among patients with a negative SLN biopsy result. In addition, eradication of axillary disease, as may occur with axillary dissection, may affect long-term survival. This concept is supported by the results of recent clinical trials demonstrating that effective local-regional control (i.e., radiation to the chest wall, axilla and internal mammary areas after axillary dissection) in women receiving adjuvant systemic therapy can improve survival (level I evidence).⁶⁻⁸

In summary, the technique for identifying the SLN has been well studied. In experienced hands, the rate of identifying the SLN is high and the false-negative rate low. What is unknown is whether or not control in the axilla or long-term survival will be as good as that with a level 1 and 2 axillary dissection. (Note: The axilla is commonly divided into 3 levels: level 1 is inferior and lateral to the pectoralis minor muscle, level 2 is beneath the pectoralis minor muscle, and level 3 is superior and medial to the pectoralis minor muscle. The standard axillary dissection removes the level 1 and level 2 nodes.) Women facing this decision must be made aware of this uncertainty.

Making treatment decisions

Adoption of procedure

- **Before surgeons replace axillary dissection by SLN biopsy as the staging procedure at their institution, they should (a) familiarize themselves with the literature on the topic and the techniques needed to perform the procedure, (b) follow a defined protocol for all 3 aspects of the procedure (nuclear medicine, surgery, pathology) and (c) perform backup**

axillary dissection until an acceptable success rate (determined by the identification of the SLN and the false-negative rate) is achieved.

- A surgeon who performs breast cancer surgery infrequently should not perform SLN biopsy.
- A positive SLN biopsy result or failure to identify an SLN should prompt full axillary dissection.
- SLN biopsy is contraindicated in women who have clinically palpable nodes, locally advanced breast cancer, multifocal tumours, previous breast surgery or previous irradiation of the breast.

Surgeons who wish to use SLN biopsy as the only surgical staging procedure for invasive breast cancer should satisfy the following 3 requirements:

- Surgeons should thoroughly familiarize themselves with the literature on the topic and the technique needed to perform successful SLN biopsy. One way of doing this is to attend a continuing medical education course or workshop featuring SLN biopsy. A visiting surgeon experienced in SLN biopsy may be very helpful.
- Surgeons should follow a defined protocol for each of the 3 aspects of the procedure (nuclear medicine, surgery and pathology). While the technique remains under development at their institution, the procedure might be designated “investigational” and could be placed under the surveillance of their institutional review board.⁶⁷
- Initially, surgeons should always perform backup axillary dissection when doing an SLN biopsy. There is no gold standard on the number of cases that should be done with backup axillary dissection. The steering committee felt that the criteria first put forward by the American Society of Breast Surgeons and endorsed by the American College of Surgeons Oncology Group⁶⁸ are reasonable: performance of 30 SLN biopsies followed by complete axillary dissection, with an 85% success rate in identifying the SLN and a 5% or lower false-negative rate. Of these 30 cases, at least 10 should have metastatic disease in the axilla. (Note: Even with 30 cases, the confidence limits around an observed rate are very wide.) Performance of fewer than 30 SLN biopsies could be considered in the context of a randomized controlled trial in which quality control is monitored by an external agency.

The performance of SLN biopsy requires a dedicated and experienced team from surgery, pathology and nuclear medicine. There are data from case series that show that the success rate in identifying the SLN is related to surgical volume,¹²⁻¹⁵ and there are some data from health services research that show a relation between surgical volume and outcome (level V evidence).⁶⁹⁻⁷¹ On the basis of these considerations the steering committee felt it was reasonable to recommend that a surgeon who performs breast cancer surgery infrequently should not perform SLN biopsy.

Histologic staining

- Staining of tissue sections with hematoxylin and eosin, and not immunohistochemical analysis for cytokeratin, should determine adjuvant therapy.

Serial sectioning of the 1 or 2 SLNs analyzed immunohistochemically for cytokeratin has yielded larger numbers of “metastases” than has routine staining with hematoxylin and eosin. The increased frequency of metastases in the nodes does not correspond to the natural history of the tumours studied. For example, in one study, 5 of 6 patients with tumours less than 0.5 cm in diameter had positive results of staining for cytokeratin in the SLN, substantially greater than the incidence of positive SLNs detected with hematoxylin and eosin staining in tumours greater than 0.5 cm in diameter (level V evidence).⁷² Cytokeratin-positive cells deserve caution in interpretation because they have been found in bone marrow samples of 23% of patients with tumours less than 0.5 cm in diameter and in 35% of patients with tumours between 0.5 cm and 1.0 cm in diameter (level V evidence).⁷³ The majority of these cells may not be clinically significant. They may in fact not be malignant.^{74,75} At this juncture the independent prognostic significance of isolated tumour cells identified by immunohistochemistry in axillary nodes is unclear.⁷⁶ It is important to realize that the clinical trials that have provided the data supporting the effectiveness of adjuvant systemic therapy (chemotherapy or tamoxifen therapy, or both) enrolled patients whose nodes removed by axillary dissection underwent traditional hematoxylin and eosin staining. Hence, there are insufficient data available on the natural history of breast tumours when metastases to sentinel axillary nodes are identified only by immunohistochemical stains for cytokeratin.

Trials underway

- Participation in randomized trials is encouraged.

Many questions remain unanswered about SLN biopsy. What is its effect on survival and on local control of cancer in the axilla? Is a full axillary dissection or systemic adjuvant therapy necessary with a positive SLN node detected by means of immunohistochemical staining only? What should be done with SLNs in the internal mammary chain?

Randomized trials that will look at these and other issues are underway. In the National Surgical Adjuvant Breast and Bowel Project B-32 trial, 4000 women with operable breast cancer will be assigned to undergo either SLN biopsy followed by axillary dissection or SLN examination followed by axillary node dissection only if the SLN is positive or if it is not identified. In 2 trials conducted by the American College of Surgeons Oncology Group (Z0010 and Z0011), 7600 women will be enlisted to undergo SLN biopsy. Patients with a negative biopsy result or those whose SLN is positive only by immunohistochemistry will be followed.

Patients with a positive SLN biopsy result (estimated to be 1900 patients) will be randomly assigned to full axillary dissection or no further axillary intervention. Participation in such trials is encouraged.

While these trials are underway and outstanding questions are being answered, SLN biopsy needs to be introduced into medical practice in a safe and organized manner.

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Contributors: There are 4 principal authors of this guideline article. The Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer provided scientific and editorial comments, which led to multiple revisions of the manuscript.

References

- Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer. *CMAJ* 1998;158(3 Suppl). Available: www.cma.ca/cmaj/vol-158/issue-3/breastcpg/index.htm
- McCready DR, Bodurtha AJ, Davis NL, Meterissian S, Robert J, Temple WJ. Sentinel lymph node biopsy in breast cancer. *Can J Surg* 1999;42:406-7.
- Spillane AJ, Sacks NP. Role of axillary surgery in early breast cancer: review of the current evidence. *Aust N Z J Surg* 2000;70:515-24.
- Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989;95(Suppl):2S-4S.
- Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 4. Axillary dissection. *CMAJ* 1998;158(3 Suppl):S22-6. Available: www.cma.ca/cmaj/vol-158/issue-3/breastcpg/index.htm
- Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949-55.
- Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997;337:956-62.
- Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353:1641-8.
- Harris SR, Hugi MR, Olivetto IA, Levine M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema. *CMAJ* 2001;164:191-9. Available: www.cma.ca/cmaj/vol-164/issue-2/0191.htm
- Schrenk P, Rieger R, Shaniyeh A, Wayand W. Morbidity following lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. *Cancer* 2000;88:608-14.
- Carter CL, Allen C, Henson DE. Relation of tumour size, lymph node status and survival in 24740 breast cancer cases. *Cancer* 1989;63:181-7.
- Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997;15:2345-60.
- In: Rosen DF, editor. *Breast cancer*. Philadelphia: Churchill Livingstone; 1999. p. 253-8.
- Morrow M, Rademaker AW, Bethke KP, Talamonti MS, Dawes LG, Clauson J, et al. Learning sentinel biopsy: results of a prospective randomized trial of two techniques. *Surgery* 1999;126:714-22.
- Cox CE, Bass S, McCann C, Wang J, Bolano M, Durand K, et al. Learning curves for sentinel lymph node mapping breast cancer base on surgical volume analysis. Society of Surgical Oncology meeting; 2000 Mar 16-19; New Orleans.
- Crossin JA, Johnson C, Stewart PB, Turner WW. Gamma-probe-guided resection of the sentinel lymph node in breast cancer. *Am Surg* 1998;7:666-9.
- Krag DN, Weaver DL, Ashikaga T, Moffat F, Klimberg VS, Shriver C, et al. The sentinel node in breast cancer: a multicenter validation study. *N Engl J Med* 1998;339:941-6.
- Barnwell JM, Arrendondo MA, Kollmorgen D, Gibbs JF, Lamonica D, Carson W, et al. Sentinel node biopsy in breast cancer. *Ann Surg Oncol* 1998;5:126-30.
- Offodile R, Hoh C, Barsky SH, Nelson SD, Elashoff R, Eilber FR, et al. Minimally invasive breast cancer staging using lymphatic mapping with radiolabeled dextran. *Cancer* 1998;82:1704-8.
- Nwariaku FE, Euhus DM, Beitsch PD, Clifford E, Erdman W, Mathews D, et al. Sentinel lymph node biopsy, an alternative to elective axillary dissection for breast cancer. *Am J Surg* 1998;176:529-31.
- De Cicco C, Cremonesi M, Luini A, Bartolomei M, Grana C, Prisco G, et al. Lymphoscintigraphy and radioguided biopsy of the sentinel axillary node in breast cancer. *J Nucl Med* 1998;39:2080-4.
- De Cicco C, Chinol M, Paganelli G. Intraoperative localization of the sentinel node in breast cancer: technical aspects of lymphoscintigraphic methods. *Semin Surg Oncol* 1998;15:268-71.
- Snider H, Dowlathshahi K, Fan M, Bridger WM, Rayudu G, Oleske D. Sentinel node biopsy in the staging of breast cancer. *Am J Surg* 1998;176:305-10.
- Gulec SA, Moffat FL, Carrol RG, Serafini AN, Sfakianakis GN, Allen L, et al. Sentinel lymph node localization in early breast cancer. *J Nucl Med* 1998;8:1388-93.
- Ratanawichitrasin A, Levy L, Myles J, Crowe JP. Experience with lymphatic mapping in breast cancer using isosulfan blue dye. *J Womens Health* 1998;7:873-7.
- Imoto S, Hasebe T. Initial experience with sentinel node biopsy in breast cancer at the National Cancer Center Hospital East. *Jpn J Clin Oncol* 1999;29:11-5.
- Miner TJ, Shriver CD, Jaques DP, Maniscalco-Theberge ME, Krag DN. Ultrasonographically guided injection improves localization of the radiolabeled sentinel lymph node in breast cancer. *Ann Surg Oncol* 1998;5:315-21.
- Sandrucci S, Mussa A. Sentinel lymph node biopsy and axillary staging of T1-T2 N0 breast cancer: a multicenter study. *Semin Surg Oncol* 1998;15:278-83.
- Paganelli G, De Cicco C, Cremonesi M, Prisco G, Calza P, Luini A, et al. Optimized sentinel node scintigraphy in breast cancer. *Q J Nucl Med* 1998;42:49-53.
- Kapteijn BAE, Nieweg OE, Petersen JL, Rutgers EJT, Hart AA, van Dongen JA, et al. Identification and biopsy of the sentinel lymph node in breast cancer. *Eur J Surg Oncol* 1998;24:427-30.
- Cox CE, Pendas S, Cox JM, Joseph E, Shons AR, Yeatman T, et al. Guidelines for sentinel node biopsy and lymphatic mapping of patients with breast cancer. *Ann Surg* 1998;227:645-53.
- O'Hea BJ, Hill ADK, El-Shirbiny A, Yeh SD, Rosen PP, Coit DG, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. *J Am Coll Surg* 1998;186:423-7.
- Pijpers R, Meijer S, Hoekstra OS, Collet GJ, Comans EF, Boom RP, et al. Impact of lymphoscintigraphy on sentinel node identification with technetium-99m-colloidal albumin in breast cancer. *J Nucl Med* 1997;38:366-8.
- Rubio IT, Korourian S, Cowan CC, Krag DN, Colvert M, Klimberg S. Sentinel lymph node biopsy for staging breast cancer. *Am J Surg* 1998;176:532-7.
- Turner RR, Olila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg* 1997;226:271-8.
- Flett MM, Going JJ, Stanton PD, Cooke TG. Sentinel node localization in patients with breast cancer. *Br J Surg* 1998;85:991-3.
- Guenther JM, Krishnamoorthy M, Tan LR. Sentinel lymphadenectomy for breast cancer in a community managed care setting. *Cancer J Sci Am* 1997;3:336-40.
- Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrada S, Bedoni M, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 1997;349:1864-7.
- Borgstein PJ, Pijpers R, Comans EF, van Diest PJ, Boom RP, Meijer S, et al. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. *J Am Coll Surg* 1998;186:275-83.
- Alex JC, Krag DN. The gamma-probe-guided resection of radiolabeled primary lymph nodes. *Surg Oncol Clin N Am* 1996;5:33-41.
- Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996;276:1818-22.
- Rodier JF, Janser JC, Barlier-Pagel C, Ghnassia J, Velten M. Sentinel axillary lymphadenectomy with intraoperative lymphatic mapping in breast cancer. *Adv Ther* 1996;13:347-54.
- Giuliano AE, Barth M, Spivack B, Beitsch PD, Evans SW. Incidence and predictors of axillary metastasis in T1 carcinoma of the breast. *J Am Coll Surg* 1996;183:185-9.
- Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;220:391-8.
- Ratanawichitrasin A, Biscotti CV, Levy L, Crowe JP. Touch imprint cytological analysis of sentinel lymph nodes for detecting axillary metastases in patients with breast cancer. *Br J Surg* 1999;86:1346-9.
- Cserni G, Boross G, Baltas B. Value of axillary sentinel nodal status in breast cancer. *World J Surg* 2000;24:341-4.
- Haigh PI, Hansen NM, Qi K, Giuliano AE. Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer. *Ann Surg Oncol* 2000;7:21-7.
- Molland JG, Dias MM, Gillett DJ. Sentinel node biopsy in breast cancer: results of 103 cases. *Aust N Z J Surg* 2000;70:98-102.
- Kollias J, Gill PG, Chatterton BE, Hall VE, Bochner MA, Coventry BJ, et al. Reliability of sentinel node status in predicting axillary lymph node involvement in breast cancer. *Med J Aust* 1999;171:461-5.
- Czerniecki BJ, Scheff AM, Callans LS, Spitz FR, Bedrosian I, Conant EF, et al. Immunohistochemistry with Pancytokeratins improves the sensitivity of sentinel lymph node biopsy in patients with breast carcinoma. *Cancer* 1999;85:1098-103.

51. Kern KA. Sentinel lymph node mapping in breast cancer using subareolar injection of blue dye. *J Am Coll Surg* 1999;189:539-45.
52. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 1993;2:335-40.
53. Bass SS, Cox CE, Ku NN, Berman C, Reintgen DS. The role of sentinel lymph node biopsy in breast cancer. *J Am Coll Surg* 1999;189:183-94.
54. Weaver DL, Krag DN, Takamura A, Seth PH, O'Connell M. Pathologic analysis of sentinel and nonsentinel lymph nodes in breast carcinoma. *Cancer* 2000;88:1099-107.
55. Krag DN, Ashikaga T, Harlow SP, Weaver DL. Development of sentinel node targeting technique in breast cancer patients. *Breast J* 1998;4:67-74.
56. Roumen RMH, Valkenburg JGM, Geuskens LM. Lymphoscintigraphy and feasibility of sentinel node biopsy in 83 patients with primary breast cancer. *Eur J Surg Oncol* 1997;23:495-502.
57. Hill ADK, Tran KN, Akhurst T, Yeung H, Yeh SDJ, Rosen PP, et al. Lessons learned from 500 cases of lymphatic mapping for breast cancer. *Ann Surg* 1999;229:528-35.
58. Bobin JY, Zinzindohoue C, Isaac S, Saadat M, Roy P. Tagging sentinel lymph nodes: a study of 100 patients with breast cancer. *Eur J Cancer* 1999;35:569-73.
59. McMasters KM, Tuttle TM, Carlson DJ, Brown CM, Noyes RD, Glaser RL, et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. *J Clin Oncol* 2000;18:2546-6.
60. Morgan A, Howisey RL, Aldape HC, Patton RG, Rowbotham RK, Schmidt EK, et al. Initial experience in a community hospital with sentinel lymph node mapping and biopsy for evaluation of axillary lymph node status in palpable invasive breast cancer. *J Surg Oncol* 1999;72:24-31.
61. Imoto S, Fukukita H, Murakami K, Ikeda H, Moriyama N. Pilot study on sentinel node biopsy in breast cancer. *J Surg Oncol* 2000;73:130-3.
62. Doting MH, Jansen L, Nieweg OE, Piers DA, Tiebosch AT, Koops HS, et al. Lymphatic mapping with intraliesional tracer administration in breast carcinoma patients. *Cancer* 2000;11:2546-52.
63. Martin RC, Edwards MJ, Wong SL, Tuttle TM, Carlson DJ, Brown CM, et al. Practical guidelines for optimal gamma probe detection of sentinel lymph nodes in breast cancer: results of a multi-institutional study. For the University of Louisville Breast Cancer Study Group. *Surgery* 2000;128:139-44.
64. Lauridsen MC, Garne JP, Hessov IP, Sorensen FB, Melsen F, Lernevall A, et al. Sentinel lymph node biopsy in breast cancer. *Acta Oncol* 2000;39:421-2.
65. Cox CE, Bass SS, McCann CR, Ku NN, Berman C, Durand K, et al. Lymphatic mapping and sentinel node biopsy in patients with breast cancer. *Annu Rev Med* 2000;51:525-42.
66. Ilum L, Bak M, Olsen KE, Kryh D, Berg V, Axelsson CK. Sentinel node localization in breast cancer patients using intradermal dye injection. *Acta Oncol* 2000;39:423-8.
67. Cody HS. Management of the axilla in early stage breast cancer: will sentinel node biopsy end the debate. *J Surg Oncol* 1999;71:137-9.
68. American Society of Breast Surgeons. *Revised consensus statement on guidelines for performance of sentinel lymphadenectomy for breast cancer*. 2000 Aug 25. Available: www.breastsurgeons.org/sentinel.htm (accessed 2001 June 25).
69. Chaudhry R, Goel V, Sawka C. Breast cancer survival by teaching status of the initial treating hospital. *CMAJ* 2001;164(2):183-8. Available: www.cma.ca/cmaj/vol-164/issue-2/0183.htm
70. Luft HS, Hunt SS, Maerki SC. The volume-outcome relationship: practice-makes-perfect or selective-referral patterns? *Health Serv Res* 1987;22:157-82.
71. Grilli R, Minozzi S, Tinazzi A, Labianca R, Sheldon TA, Liberati A. Do specialists do it better? The impact of specialization on the process and outcomes of care for cancer patients. *Ann Oncol* 1998;9:365-74.
72. Dowlatsahi K, Fan M, Bloom KJ, Spitz DJ, Pavel S, Snider HC Jr. Occult metastases in the sentinel lymph nodes of patients with early stage breast cancer. *Cancer* 1999;86:990-6.
73. Braun S, Pantel K, Muller P, Janni W, Hepp F, Kentemichi CR, et al. Cytokeratin positive cells in the bone marrow and survival of patients with stage I, II or III breast cancer. *N Engl J Med* 2000;342:525-33.
74. Borgen E, Beiske K, Trachsel S, Nesland JM, Kvalheim G, Herstad TK, et al. Immunocytochemical detection of isolated epithelial cells in bone marrow: non-specific staining and contribution by plasma cells directly reactive to alkaline phosphatase. *J Pathol* 1998;185:427-34.
75. Lambrechts AC, Bosma AJ, Klaver SG, Top B, Perebolte L, van't Veer LJ, et al. Comparison of immunocytochemistry, reverse transcriptase polymerase chain reaction, and nucleic acid sequence-based amplification for the detection of circulating breast cancer cells. *Breast Cancer Res Treat* 1999;56:219-31.
76. Hermanek P, Hutter RV, Sobin LH, Wittekind C. Classification of isolated tumor cells and micrometastasis. *Cancer* 1999;86:2668-73.

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A patient guide to sentinel lymph node biopsy appears on page 172.

Appendix 1

Questions and answers on sentinel lymph node biopsy

A guide for women and their physicians

I am about to begin treatment for breast cancer. What surgical procedures are used to find out if cancer has spread to my lymph nodes?

The most commonly used method for determining the extent or “stage” of a breast cancer is “axillary dissection” — a surgical procedure that involves removing and examining lymph nodes (sometimes called “glands”) from the armpit (see guideline 4 on the removal of lymph nodes during breast cancer surgery [www.cma.ca/cmaj/vol-158/issue-3/breastcpg/0022.htm]).

“Sentinel lymph node biopsy” is an alternative staging method. It is a newer surgical procedure that involves removal and examination of 1 or 2 lymph nodes identified as the most important in the area where the cancer was found.

Why are lymph nodes removed?

Lymph nodes are part of the system that carries a fluid called “lymph” around the body. When breast cancer spreads, cancer cells often collect in the lymph nodes in the armpit. By removing some of the lymph nodes in the armpit and examining them under a microscope, doctors can obtain important information about how far the cancer has progressed. Information on whether the nodes are “positive” (contain cancer cells) or “negative” (do not contain cancer cells) will help determine the right treatment for you after surgery (see guideline 7 [www.cma.ca/cmaj/vol-164/issue-2/breastcpg/guideline7rev.htm] and guideline 8 [www.cma.ca/cmaj/vol-164/issue-5/breastcpg/guideline8rev.htm]). Removal of lymph nodes also reduces the risk that cancer will come back in the armpit area.

What is sentinel lymph node biopsy?

During a sentinel lymph node biopsy, radioactive material or a dye, or both, is injected into the breast tissue surrounding the tumour or the place where the tumour was removed. As the lymph carries the material or dye through the lymphatic pathways, the surgeon uses a device to identify the first node the lymph reaches (the “sentinel lymph node”), which is then removed by the surgeon for examination in the laboratory by a pathologist.

If the sentinel lymph node is found to be positive (to contain cancer cells), this suggests that other nodes in the area may be positive. If the sentinel lymph node is found to be negative (not to contain cancer cells) this suggests that other nodes in the area are also negative. Thus, the sentinel lymph node is thought to accurately reflect the state of all the nodes in the armpit.

What are the benefits of sentinel lymph node biopsy?

If you have sentinel lymph node biopsy you may avoid some of the side effects related to axillary dissection. These side effects include restriction of shoulder movement, pain, numbness and lymphedema (arm swelling) (see guideline 4

[www.cma.ca/cmaj/vol-158/issue-3/breastcpg/0022.htm] and guideline 11 [www.cma.ca/cmaj/vol-164/issue-2/0191.htm]).

What are the disadvantages of sentinel lymph node biopsy?

When a sentinel lymph node biopsy is performed, there is a small chance, usually less than 10%, that even though no cancer cells are found in the sentinel lymph node, cancer cells are present in other lymph nodes in the armpit. You should be aware that missing these cancer cells may affect the treatment you receive after surgery and the chance of breast cancer returning.

What should be done if the sentinel lymph node is negative for cancer?

If the sentinel lymph node is found to be negative, further surgical procedures are not required for staging the cancer.

What should be done if the sentinel lymph node is positive for cancer?

If the sentinel lymph node is found to be positive, this suggests that other lymph nodes in the armpit may contain cancer cells and an axillary dissection should be done.

What are some of the questions you should ask your surgeon about sentinel lymph node biopsy?

Sentinel lymph node biopsy is a challenging procedure to perform and is only mastered with experience. This means that medical specialists who have not performed a large number of these biopsies may have a high failure rate; that is, they will not be able to accurately and consistently identify the sentinel lymph node and determine whether it does or does not contain cancer cells. You should ask your surgeon the following questions:

- *How often do you perform breast cancer surgery? A surgeon who does not perform breast cancer surgery frequently should not do sentinel lymph node biopsy.*
- *How many sentinel lymph node biopsies have you performed, and what is your success rate with the procedure? Surgeons offering to perform this procedure should inform patients of the number of biopsies they have completed and the number of times they have correctly identified the sentinel lymph node. They should indicate the number of times they have found cancer cells in the lymph nodes in the armpit when the sentinel lymph node was negative.*

When surgeons first start performing sentinel lymph node biopsy, they should also perform back-up axillary dissection on all patients. It has been suggested that, before a surgeon

performs sentinel lymph node biopsy alone (without axillary dissection), he or she should have performed at least 30 sentinel lymph node biopsies followed by axillary dissection. In these 30 cases, the surgeon should have identified the sentinel lymph node at least 85% of the time and found cancer cells in the nodes under the arm in no more than 5% of cases when the sentinel lymph node was negative.

When should sentinel lymph node biopsy *not* be performed?

If you have had breast surgery or radiation to the breast in the past, you should not have sentinel lymph node biopsy. You should also not have the biopsy procedure if you have "clinically palpable nodes" (lymph nodes that your doctor can


feel), "locally advanced breast disease" (very extensive cancer in the breast) or tumours in more than one location in the breast, or if you have had breast reduction surgery in the past.

Should I have sentinel lymph node biopsy instead of axillary dissection?

You will need to discuss this question with your doctor and the other medical specialists involved in your care. Axillary dissection is still the most widely accepted treatment for the surgical staging of breast cancer. You and your doctor will need to discuss what is and is not known about sentinel lymph node biopsy before you make a decision about which procedure is best for you. You may choose to participate in a clinical research trial of sentinel lymph node biopsy.

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