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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer

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ABSTRACT

Purpose
To develop a guideline for the use of sentinel node biopsy (SNB) in early stage breast cancer.

Methods
An American Society of Clinical Oncology (ASCO) Expert Panel conducted a systematic review of the literature available through February 2004 on the use of SNB in early-stage breast cancer. The panel developed a guideline for clinicians and patients regarding the appropriate use of a sentinel lymph node identification and sampling procedure from hereon referred to as SNB. The guideline was reviewed by selected experts in the field and the ASCO Health Services Committee and was approved by the ASCO Board of Directors.

Results
The literature review identified one published prospective randomized controlled trial in which SNB was compared with axillary lymph node dissection (ALND), four limited meta-analyses, and 69 published single-institution and multicenter trials in which the test performance of SNB was evaluated with respect to the results of ALND (completion axillary dissection). There are currently no data on the effect of SLN biopsy on long-term survival of patients with breast cancer. However, a review of the available evidence demonstrates that, when performed by experienced clinicians, SNB appears to be a safe and acceptably accurate method for identifying early-stage breast cancer without involvement of the axillary lymph nodes.

Conclusion
SNB is an appropriate initial alternative to routine staging ALND for patients with early-stage breast cancer with clinically negative axillary nodes. Completion ALND remains standard treatment for patients with axillary metastases identified on SNB. Appropriately identified patients with negative results of SNB, when done under the direction of an experienced surgeon, need not have completion ALND. Isolated cancer cells detected by pathologic examination of the SLN with use of specialized techniques are currently of unknown clinical significance. Although such specialized techniques are often used, they are not a required part of SLN evaluation for breast cancer at this time. Data suggest that SNB is associated with less morbidity than ALND, but the comparative effects of these two approaches on tumor recurrence or patient survival are unknown.

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INTRODUCTION

The disease status of the axillary lymph nodes is the most significant prognostic factor for patients with early-stage breast cancer. Predictors of node metastases include tumor size, lymphovascular invasion, tumor grade, and patient age. Receptor status,

DNA content (ploidy), tumor location, method of detection, and presence of casting-type calcifications on mammography have some predictive value.[1-6] However, no combination of predictors of axillary node status has replaced surgical resection and histopathologic examination of the lymph nodes.[7] The use of mammography and increased public awareness of breast cancer have resulted in women having smaller tumors at the time of initial presentation, a lower risk of involved nodes, and fewer involved nodes.[8,9] Similarly, while advances in computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasonography can often identify suspicious nodes in the axilla, false-negative findings and failure to detect small metastases are common. Thus, reliance on histologic examination of removed lymph nodes at the time of axillary lymph node dissection (ALND) is thought to be the most accurate method for assessing spread of disease to the lymph nodes. Accurate assessment of the nodes is important not only for staging and prognosis, but also for guiding treatment selection.

However, the anatomic disruption caused by ALND may also result in lymphedema, nerve injury, shoulder dysfunction, and other complications that may compromise functionality and quality of life. Systematic studies in breast cancer have shown that breast cancer spreads to one or a few lymph nodes, the sentinel lymph node(s) (SLNs), before it spreads to other axillary nodes and that these SLNs can be identified by using vital blue dye, a radiolabeled colloid, or both.[10,11] The findings of these early studies suggested that the use of a sentinel lymph node identification and sampling procedure referred to here as sentinel node biopsy (SNB) could be reliably performed in selected patients with early stage breast cancer by a carefully trained multidisciplinary team (surgeon, pathologist, nuclear medicine technician), thus reducing the need for ALND and avoiding the associated morbidity.[10-22] Despite few controlled clinical studies of SNB, this procedure has become widely practiced in the United States, Europe, and Australia. Currently, at most major cancer centers in the United States, SNB is performed without ALND if no disease is found in the SLN.[23] The American Society of Clinical Oncology (ASCO) convened an Expert Panel to develop recommendations for the use of SNB in oncology practice and to determine its suitability in the staging and management of early stage breast cancer.

GUIDELINE QUESTIONS

This guideline addresses four principal questions regarding the appropriateness of SNB for the management of early stage breast cancer:

1. How should the results of SNB be utilized in clinical practice?

a. Can full ALND be avoided in patients who have negative findings on SNB?

b. Is full ALND necessary for all patients with positive findings on SNB?

2. What is the role of SNB in special circumstances in clinical practice? (These special circumstances include large and locally advanced invasive tumors, multicentric tumors, 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.)

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?

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide the following:

1. Improvement in outcomes
2. Improvement in medical practice
3. Means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where further research is needed

In formulating recommendations for the appropriate use of the SNB in the management of early stage breast cancer, ASCO considered these tenets of guideline development, emphasizing review of data from appropriately conducted and analyzed clinical trials. However, it is important to note that guidelines cannot always account for individual variation among patients. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result.

Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe the use of procedures and therapies in clinical practice; they cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions and settings for further research.

METHODS

Panel Composition

The ASCO Health Services Committee (HSC) convened an Expert Panel consisting of experts in clinical medicine and research relevant to breast cancer management, including surgical oncology, pathology, radiation oncology, and medical oncology. Academic and community practitioners, an oncology fellow, and a patient representative were also part of the Panel. The Panel members are listed in Appendix 1.

Literature Review and Analysis

The SNB is primarily a staging procedure and, in numerous studies, its test accuracy has been based on comparison with completion ALND dissection as the gold standard. As such, randomized controlled trials (RCTs) have not been thought necessary to define the staging accuracy of SNB. RCTs are necessary, however, to determine the effect of SNB compared with that of axillary dissection on subsequent clinical management and long-term benefits and harms, including the clinical, quality-of-life, and economic impact on patients with early-stage breast cancer. While ASCO awaits the results of RCTs, the complexities, limitations, and variability of SNB performance prompted the Society's current effort to develop a Clinical Practice Guideline for the interpretation and application of this procedure in clinical oncology.

Three systematic reviews with formal statistical meta-analysis have been published previously.[24-26] Each of these reviews was based on data from a limited and selected number of existing studies. In an effort to evaluate more fully the published results of SNB, an expanded systematic review of published literature of SNB test performance has been conducted by members of the ASCO Guidelines Panel.[24,27] This review utilized electronic techniques (Medline, the Cochrane Library, Best Evidence [ACP Journal Club and Evidence-Based Medicine], DARE [Database of Abstract of Reviews of Effectiveness], Dissertation Abstracts) and hand-searching techniques. Only studies incorporating full lymph node dissection, regardless of the results of SNB were included. Between 1994 and 2004, 69 trials that met eligibility criteria were reported. Study quality was evaluated by two blinded observers on a 5-point modified scale with factors of description of patient characteristics, reason for study withdrawal, test performance measures, measures of variability, and a description of the SNB technique. The relationships of the rate of false-negative findings, predictive value, and the proportion of successful lymphatic mappings to study size, the proportion of patients with positive lymph nodes, the technique used, and study quality were evaluated.

Consensus Development Based on Evidence

The entire Panel met twice; additional work on the guideline was completed through teleconferences of a steering group of the Panel. The purposes of the Panel meetings were to refine the questions addressed by the guideline and to make writing assignments for the respective sections. All members of the Panel participated in the preparation of the draft guideline, which was then disseminated for review by the entire Panel. Feedback from external reviewers was also solicited. The content of the guideline and the manuscript were reviewed and approved by the HSC and by the ASCO Board of Directors before dissemination.

Guideline and Conflict of Interest

All members of the Expert Panel complied with ASCO policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Revision Dates

At annual intervals, the Panel Co-Chairs and two Panel members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guideline to the HSC and the ASCO Board for review and approval.

Definition of Terms

Axillary lymph node dissection (ALND): surgical resection and histopathologic examination of lymph nodes contained in the axillary basin. In current practice, this routinely includes axillary level I and II nodes; level III nodes are optionally removed after intraoperative palpation of the region. (Also referred to as axillary dissection.)

Lymphatic mapping: the use of blue dye, radiolabeled colloid, or both, to identify the drainage pattern of the breast, generally with the intent of identifying the SLN(s).

Sentinel lymph node (SLN): the first lymph node or group of lymph nodes encountered in the lymphatic drainage of the breast, generally identified by lymphatic mapping. Some consider suspicious nodes found at the time of SNB as SLNs as well.

Sentinel node biopsy (SNB): the surgical removal and histopathologic examination of the SLN.

Summary of Outcomes Assessed

Important measures for assessing SNB include the following:

1. 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.

2. The false-negative rate represents the proportion of patients with negative findings on SNB who are subsequently found to have disease in the axillary lymph nodes on ALND. An intraoperative false-negative finding represents a SLN 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 SLN but findings of metastases by full ALND.

3. The negative predictive value is the proportion of individuals with negative findings of SNB in whom no involvement of the axillary lymph nodes is found on ALND.

4. Accuracy is the proportion of all patients (positive or negative findings of SNB) for whom the SNB correctly predicts the results of ALND.

RESULTS

Literature Search

The 69 identified studies in which SNB was compared with completion ALND included 10,454 patients, 8,059 of whom completed study. The sensitivity of SNB for node involvement ranged from 71% to 100%, and the false-negative rate averaged 8.4%, ranging from 0% to 29% across all trials. The rate of false-negative findings varied according to the number of patients; the proportion of successful mappings; inclusion of patient characteristics, measures of test performance, and measures of variability; and whether blue dye or radiolabeled colloid, or both, was used (Table 1). The proportion of successful mappings was significantly higher and the false-negative rate was significantly lower in studies in which a radiolabeled colloid was used for mapping.

In summary, this systematic review demonstrates that reported measures of SNB test performance vary depending on sample size, risk, mapping technique (radioisotope, blue dye, or both) and measures of study quality. While many of these reports represent the investigators' early experience with this procedure, as a whole the findings suggest that SNB is a reasonably accurate method for assessing the status of the axillary lymph nodes in many women with early-stage breast cancer. The overall false-negative rate in the review of nonrandomized studies of test performance is virtually identical to the rate found thus far in RCTs.

Previous Consensus Statements

Consensus statements have also been developed by some professional societies, including the American Society of Breast Surgeons; the Institute for Clinical Systemic Improvement; the Canadian Steering Committee; the Consensus Conference Committee, Philadelphia; and the German Society of Senology.[28-32] Whereas the Philadelphia Consensus Conference put more emphasis on the input from experts and pioneers of the field, the other societies based their statements on a panel review of the existing literature. The Philadelphia Consensus Conference concluded that SNB could replace routine ALND for patients with no disease in the SLN, with no further axillary treatment necessary.[30]

HOW SHOULD THE RESULTS OF SNB BE UTILIZED IN CLINICAL PRACTICE?

Can Full ALND Be Avoided in Patients With Negative Findings on SNB?

Summary and recommendations. The reported test performance characteristics of SNB vary widely across studies reported in the medical literature.[24] However, when carried out by an experienced team, negative findings appear to be predictive of negative axillary nodes for most patients with breast cancer.[24] Significant predictors of post-test probability include the percentage of patients in the study population with positive axillary nodes and the proportion of successful lymphatic mappings. In addition, the incidence of axillary recurrence after negative findings on SNB is comparable to that following ALND.[10,33] On the basis of the available evidence, the Panel supports the use of SNB for staging disease in most women with clinically negative axillary lymph nodes. The concept of SNB has been so appealing to physicians and patients that the identification and biopsy of SLNs has largely replaced ALND for patients with clinically and histologically tumor-free lymph nodes. The Panel recommends that suspicious palpable nodes should also be submitted as SLNs, and that, in this context, the surgeon should have a low threshold for default to ALND, particularly for patients whose clinical presentation suggests a high risk of axillary metastasis. SNB works well, with a comparable false-negative rate in the setting of both mastectomy and breast-conserving surgery.[34,35] Nevertheless, the Panel concluded that, on the basis of the available

Table 1. False Negative Rates in Trials in Which Sentinel Lymph Node Biopsy Is Compared With Axillary Lymph Node Dissection

	False-Negative Rate (%)	*P*
All trials	8.4 (0-29)	
Trials with ≥ 100 patients *v* trials with < 100 patients	6.7 *v* 9.0	.02
Successful mapping in ≥ 90% *v* < 90%	6.3 *v* 11.1	.003
Patient characteristics (given *v* not given)	7.8 *v* 11.6	.009
Measures of test performance (given *v* not given)	7.0 *v* 10.3	.009
Measures of variability (given *v* not given)	6.2 *v* 9.0	.01
Use of both dye and radiolabeled colloid *v* use of only one	7.0 *v* 9.9	.07

literature, there are compelling reasons for the operating surgeon to default to ALND, including a failed or technically unsatisfactory SNB procedure, and the presence of clinically suspicious nodes in the axilla after the removal of all SLNs. About half of patients in whom the identified SLN proves to be falsely negative will have had clinically suspicious nodes palpable at surgery, because gross tumor involvement may interfere with the uptake of both radiolabeled colloid and dye and deviate lymph flow to a node other than the true SLN.[36,37]

Evidence from RCTs. To date, only one prospective randomized trial has been published in which SNB was compared with formal axillary dissection.[10] Veronesi et al randomly assigned 516 patients with tumors of 2 cm or less to either SNB and ALND or SNB followed by axillary dissection only if the SLN contained metastases. If lymphatic mapping failed, the patient was excluded from the study. For the patients who had SNB and ALND, the false-negative rate was 8.8% (95% CI, 3.9 to 16.6) and the negative predictive value was 95.4% (95% CI, 91.1 to 98.0). There were fewer axillary complications and less morbidity in the group that had ALND only if the SLN was positive for disease. For patients who did not have ALND, there were no axillary recurrences and the short-term survival was the same as for patients with tumor-free nodes who had an ALND. However, the median follow-up was only 46 months, and the study lacked the power to detect small differences in survival.

Several RCTs are ongoing at multiple centers in the United States and Europe. In National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32, as in the study by Veronesi et al, SNB followed by ALND is being compared with SNB and ALND only if tumor is found in the SLN. This large multi-institutional study is designed to examine the long-term survival effect of SNB alone and its morbidity compared with axillary dissection. This study has completed accrual, with 5,611 randomly assigned patients who will be evaluated over the next several years. Since completion of the planned literature review for the present guideline, the early results of NSABP B-32 were presented at a major meeting (27th Annual San Antonio Breast Cancer Symposium, December 8-11, 2004). For patients who had SNB followed by ALND, lymphatic mapping was successful in 97.1% (95% CI, 96.5 to 97.8), the false-negative rate was 9.7% (95% CI, 7.6 to 11.9), and the negative predictive value was 96.1% (95% CI, 95.2 to 97.0).[38]

While awaiting long-term follow-up from RCTs, surgeons continued to validate the test performance of SNB by performing it with an axillary dissection in the same patient. Currently, most trained and experienced surgeons at major cancer centers in the United States and Europe perform SNB alone when the SLN is found to be tumor-free by routine analysis and perform completion ALND only when the findings of SNB indicate axillary metastases.[23] Nevertheless, while the diagnostic accuracy of SNB has been demonstrated to the satisfaction of most clinicians, further RCTs are needed to evaluate the therapeutic impact and long-term outcomes associated with the procedure.

Is Full ALND Necessary for All Patients With Positive Findings on SNB?

Summary and recommendations. The recently reported meta-analysis demonstrates that, among patients with a positive SLN, 48.3% (95% CI, 35 to 62) were found to have additional node disease on ALND.[24] Thus, the Panel recommends routine ALND for patients with a positive SLN according to routine histopathologic examination. More problematic is the management of patients for whom the SLN is positive only with use of special studies, primarily immunohistochemical (IHC) analysis with antibodies to cytokeratin. IHC evaluation can upstage disease for approximately 10% of patients who have a negative SLN, but whether this conversion to a higher stage is relevant remains unknown at this time.[39-42] In the new American Joint Cancer Commission (AJCC) staging system, the node classification (pN0) is not altered by clusters of isolated tumor cells of 0.2 mm or less, regardless of the staining technique used to identify them.[43,44]

It remains unclear whether isolated tumor cells or micrometastases (lymph node metastases larger than 0.2 mm but not larger than 2 mm) detected with hematoxylin and eosin (H&E) staining or special stains represents an adverse prognostic indicator and whether ALND should be carried out in all such cases. Likewise, there are insufficient data to determine whether the presence of isolated tumor cells or micrometastases should be a factor in treatment decisions. However, metastasis is found in nonsentinel nodes in approximately 10% of patients with isolated tumor cells in the SLN and in 20% to 35% of patients with micrometastases in the SLN.[45] Until further studies addressing the clinical relevance of isolated tumor cells or micrometastases in the SLN are complete, the Panel recommends routine ALND for patients with micrometastases ($>0.2 \leq 2$ mm) found on SNB, regardless of the method of detection. Regarding the question of which patients with a positive SLN may be appropriately treated with breast or axillary radiation and which patients should have completion ALND, relevant studies have included short follow-up and small numbers of patients in retrospective series, and no results from RCTs are available. Therefore, the Panel concluded that there are insufficient data to answer this question.

Predictive models. Treatment decisions may be aided by knowing which patients with a positive SLN are likely to have additional metastatic disease found at ALND. In multivariate analysis, three pathologic factors have been identified as being significantly associated with an increased likelihood of residual involvement of a nonsentinel node in the presence of a positive SLN: size of the metastasis in the SLN (detected only by IHC analysis, micrometastasis [$>0.2 \leq 2.0$ mm], or macrometastases), primary tumor size, and

the presence of lymphovascular invasion.[46-52] By combining all three factors, involvement of a nonsentinel node can be more accurately estimated for an individual patient. Turner et al generated detailed estimates of the likelihood of involvement of a nonsentinel node in patients who had a positive SLN node for a broad range of clinical situations; these estimates may be useful in predicting the risk of residual disease in the axilla for an individual patient with a positive SLN.[48] Alternatively, Van Zee et al created a multivariate model to predict the likelihood of additional metastases that incorporates nine variables based on data from 702 patients who had a positive SLN and completion ALND. This nomogram was then prospectively validated on a subsequent population of 373 patients.[53]

Micrometastases and isolated tumor cells. Some studies have demonstrated that micrometastasis has an adverse effect on survival, whereas others have shown no effect on survival.[41,54-61] The definition of micrometastasis used in the literature has been variable and the mode of detection has been different, ranging from simple H&E staining to reverse transcriptase polymerase chain reaction, with IHC analysis used in most studies. There is only one relatively small study in which no early adverse outcome was found at a median follow-up of 38 months for patients with micrometastases detected by either H&E staining or IHC analysis.[41]

Radiation therapy compared with ALND. There have been few studies concerning which patients with a positive SLN will benefit from radiation therapy rather than completion ALND. In NSABP B-04, 818 patients with clinically node-negative disease were randomly assigned to modified radical mastectomy, total mastectomy plus radiation therapy to the axilla, or total mastectomy alone. At 10 years, the axillary recurrence rate was 3.1% for patients treated with radiation compared with 1.4% for patients treated with axillary dissection.[46] The Joint Center for Radiation Therapy reported regional node failure at 8 years in 7.1% of 42 patients with clinically node-negative disease who were found to have involved axillary nodes on pathologic evaluation and who had a limited dissection (removal of one to five nodes) and radiation therapy to the breast and regional nodes.[47]

Determining which patients with a positive SLN may benefit from radiation rather than completion ALND is complicated by the frequent use of breast tangential radiation and systemic therapy. Several small nonrandomized series with limited power have been designed to address the comparative value of radiation therapy to the regional lymph nodes. In a series from Northwestern University, 63 patients with a positive SLN who did not have ALND were treated with adjuvant radiation therapy to the breast with or without radiation directed to the regional lymph nodes.[62] At a median follow-up of 31.2 months, none of the 44 patients who had radiation to only the breast had recurrence in the axilla despite the fact that 87% of the patients had a positive SLN on IHC analysis. Among the 20 patients treated with radiation to the breast and regional nodes, all of whom had a positive SLN on H&E staining, one patient had recurrence in the axilla. In a second series from Baylor, no axillary recurrences were found at a mean follow-up of 30 months among 31 patients who had a positive SLN and refused axillary dissection.[63] All patients received systemic therapy and either breast tangential or chest wall radiation. In a third study, there were no axillary recurrences at a median follow-up of 32 months among 46 women who had a positive SLN, did not have ALND, and had radiation to the breast.[64] Therefore, radiation to the breast, with or without radiation directed specifically to the axilla, may be considered for patients with clinically negative nodes in the axilla and a positive SLN who are a poor risk for surgery or are unwilling to have additional surgery. No data exist regarding the long-term benefits and harms associated with these treatment approaches.

Ongoing studies. The NSABP B-32 trial will also determine the false-negative rate associated with SNB, as well as the rate of recurrence in the axilla and the clinical significance of occult micrometastases in SLNs classified as negative on initial evaluation but positive on more comprehensive evaluation with step sections and IHC analysis. In European Organisation for Research and Treatment of Cancer (EORTC) 10981, ALND is compared with radiation to the nodes for patients with a positive SLN. In the American College of Surgeons (ACOSOG) trial Z0011, patients with a positive SLN on H&E staining were randomly assigned to radiation to the breast only, without specific treatment to the axillary nodes, or to radiation to the breast plus axillary dissection. This study is designed to compare the efficacy of tangential radiation alone versus axillary dissection following positive results on SNB. Patients participating in this trial will be followed up, but the trial has been suspended because of low accrual and will not be able to address the original study questions.

What Is the Role of SNB in Special Circumstances in Clinical Practice?

Summary and recommendations. On the basis of the available literature, the Panel concluded that SNB is not recommended for large or locally advanced invasive breast cancers (T3 and T4); inflammatory breast cancer; DCIS, when breast-conserving surgery is to be done; pregnancy, in the setting of prior nononcologic breast surgery or axillary surgery; and in the presence of suspicious palpable axillary lymph nodes. Data are available to support the use of SNB for smaller tumors (T1 and T2); multicentric tumors; DCIS, when mastectomy or immediate reconstruction is planned; for older or obese patients; in male breast cancer; and prior excisional or diagnostic biopsy. The recommendations and levels of evidence are provided in Table 2.

Large and locally advanced invasive breast cancers. Most early studies limited the use of SNB to T1 tumors (≤ 2 cm) or T2 tumors (> 2 but < 5 cm); the Panel, therefore,

Table 2. Recommendations and Levels of Evidence

Clinical Circumstance	Recommendation for Use of Sentinel Node Biopsy	Level of Evidence*
T1 or T2 tumors	Acceptable	Good
T3 or T4 tumors	Not recommended	Insufficient
Multicentric tumors	Acceptable	Limited
Inflammatory breast cancer	Not recommended	Insufficient
DCIS with mastectomy	Acceptable	Limited
DCIS without mastectomy	Not recommended except for large DCIS (> 5 cm) on core biopsy or with suspected or proven microinvasion	Insufficient
Suspicious, palpable axillary nodes	Not recommended	Good
Older age	Acceptable	Limited
Obesity	Acceptable	Limited
Male breast cancer	Acceptable	Limited
Pregnancy	Not recommended	Insufficient
Evaluation of internal mammary lymph nodes	Acceptable	Limited
Prior diagnostic or excisional breast biopsy	Acceptable	Limited
Prior axillary surgery	Not recommended	Limited
Prior non-oncologic breast surgery (reduction or augmentation mammoplasty, breast reconstruction, etc)	Not recommended	Insufficient
After preoperative systemic therapy	Not recommended	Insufficient
Before preoperative systemic therapy	Acceptable	Limited

Abbreviations: DCIS, ductal carcinoma-in-situ; SNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.
*Levels of evidence: Good, multiple studies of SNB test performancebased on findings on completion ALND; Limited, few studies of SNB test performance based on findings on completion ALND or multiple studies of mapping success without test performance assessed; and Insufficient, no studies of SNB test performance based on findings on completion ALND and few if any studies of mapping success.

recommends consideration of the use of SNB for women with tumors smaller than 5 cm. The Panel concluded that there are currently insufficient data on SNB for women with larger tumors (T4 tumors, noninflammatory breast cancers) to suggest that the procedure is accurate in these situations. Therefore, the Panel does not recommend the routine use of SNB in these settings until more data are available. As always, clinical judgment should be used to weigh the associated benefits and risks for an individual patient and to select patients appropriate for surgical procedures.

Inflammatory breast cancer. There are insufficient data on women with inflammatory breast cancer to recommend the use of SNB in this situation. Because the subdermal lymphatics are partially obstructed, contain tumor emboli, and are functionally abnormal, the false-negative rate for SNB for this population may be unacceptably high.[65] Similarly, there are insufficient data to recommend the use of SNB for women with other T4 lesions (skin invasion and/or chest wall invasion).

Multicentric tumors. Multicentric cancer in the same breast occurs in approximately 10% of cases and is generally defined as distinct cancers occurring in separate quadrants of the breast, or at a distance of more than 2 to 5 cm from each other. Most investigators have excluded patients with multicentric lesions from SNB. More recently, several proposed techniques for performing SNB may address this issue. Initial reports of SNB in breast cancer were based on a technique involving peritumoral injection of either radiolabeled colloid[66] or blue dye.[67] Subsequent experience has shown that subdermal,[68] intradermal,[37,69] and subareolar[70,71] routes of injection are associated with greater success and a comparable false-negative rate to that associated with the peritumoral route. If indeed the same SLN is "sentinel" for the entire breast, then this SLN or SLNs can be identified in cases of multicentric cancer by subareolar or intradermal injection. Several small nonrandomized series in which such an approach was evaluated have demonstrated that the test performance of SNB is similar to that for women with unifocal disease, suggesting that the technique can be applied in this setting.[72-74]

Ductal carcinoma in situ. Axillary staging is generally not necessary for patients with DCIS as determined by biopsy results, but in certain clinical circumstances, axillary staging may be important in order to avoid a second operation. Several studies of DCIS have shown a 5% to 15% incidence of involved SLNs on the basis of IHC analysis, but the clinical significance of such metastases remains unclear.

The Panel recommends considering SNB for patients with DCIS when a mastectomy is indicated or when immediate reconstruction is planned, as axillary staging by SNB is essentially impossible if an invasive tumor is found. Although invasive cancer will be subsequently found in 10% to 20% of patients who have DCIS diagnosed by core biopsy, the Panel does not recommend routine use of SNB in patients with DCIS who are to have breast-conserving surgery. Some Panel members recommend SNB for patients with large or high-grade DCIS who are to have breast-conserving surgery or mastectomy, so as to avoid a second operation on the axilla if invasive cancer is found.

Older age and obesity. Several studies have shown that accurate identification of the SLN decreases with increasing age and body mass. The findings of a study of 1,356 patients suggested that for every increase of 1 unit of body mass index and for every increase of 1 year of age, the odds of successful SNB decreased by 0.05.[75] This trial also demonstrated that the radioactive node count of a SLN is inversely proportional to age ($P < .001$). Another study of 966 patients included a multivariate analysis that suggested that success of the SNB was greatest for women who were 60 years or younger when a combination of dye and isotope was used ($P = .033$).[34] These findings, however, do not support any contraindication for SNB in obese or older individuals.[75] As always, clinical judgment should be used to select appropriate patients for surgical procedures.

Male breast cancer. Male breast cancer is uncommon, with approximately 1,700 new cases expected annually in the United States.[76] Although the diagnosis in men is often delayed and patients often present with larger tumors, survival is similar to that for women when controlled for common prognostic factors.[77,78] Modified radical mastectomy, often followed by radiation therapy, is the procedure most commonly recommended.[79-81] The risk of local complications (eg, hematoma and seroma) is greater for men,[82] but the risk of lymphedema following axillary node dissection is similar to that for women. Data on the use of SNB in men with breast cancer are limited, except for a few anecdotal reports[82-84] and small institutional series.[85,86] Port et al reported that the SLN was identified in 15 of 16 men with early-stage breast cancer who had SNB at Memorial Sloan-Kettering Cancer Center between 1996 and 1999.[85] Albo et al reported that the SLN was identified in all 7 men who had the procedure at M.D. Anderson Cancer Center between October 1999 and 2000.[86] Lymphedema developed in one of the four patients who also had an ALND. Therefore, although the data are limited, the treatment of male breast cancer has paralleled that of female breast cancer, and the Panel believes that it is unlikely that SNB will be any less accurate in men than it is in women. The Panel concludes that there are limited data to make categoric recommendations about the use of SNB for men with breast cancer.

Pregnancy. The safety and test performance of SNB during pregnancy has not been fully evaluated. Vital dyes should not be administered to pregnant women; however, radiolabeled colloids are most likely safe because of the rapid uptake into the reticuloendothelial system of any material that enters circulation. Recent data demonstrate that the dose of radiation to the fetus is minimal, allowing reasonable consideration of SNB during pregnancy.[87] Nevertheless, the Panel concludes that there are insufficient data at this time to recommend the use of SNB in pregnant women with breast cancer.

Evaluation of internal mammary lymph nodes. Radical resection of the internal mammary lymph nodes offers no survival advantage over conventional surgery, and untreated internal mammary nodes are rarely a source of local recurrence in patients with early stage breast cancer.[88] The significance of internal mammary node involvement is therefore largely prognostic and comparable to that of positive axillary nodes.[89,90] The discovery of a positive internal mammary node benefits only those patients who are not otherwise candidates for adjuvant systemic therapy. The likelihood of internal mammary lymph node involvement in such patients is approximately 10% whether the tumor is located medially or laterally.[91] Two studies documented the presence of nonaxillary SLNs in 19% to 25% of all patients with breast cancer, but metastasis was limited to the internal mammary nodes in only 1.3% of the women.[92,93] Although SNB of internal mammary nodes may be useful in some instances, the decision to perform the procedure should be determined on the basis of the clinical judgment of the treating physicians. The Panel concludes that there are limited data on the use of SNB to evaluate internal mammary nodes.

Prior breast or axillary surgery. The impact of prior breast or axillary surgery on the successful identification of SLNs has not been well characterized. Many of the seminal reports on SNB excluded patients with previous excisional biopsy[10,15,68,94] and/or previous axillary surgery.[7,95] Limited data suggest that the biopsy method, in particular, excisional biopsy, does not affect the success of SNB.[96] In a retrospective study of 181 patients who were evaluated at a single cancer center, excision done at some time before SNB did not affect the subsequent identification rate of SLNs. Similarly, neither the volume of the excisional biopsy specimen nor the interval from the biopsy to the SNB affected the identification rate. On the basis of these data and accumulated clinical experience, the Panel concluded that prior diagnostic or excisional breast biopsy is not a contraindication to SNB.[30,97]

However, the feasibility of SNB has not been evaluated for women who have had another, nononcologic breast surgery, such as reduction or augmentation mammoplasty, or breast reconstruction. It is likely that more extensive breast and/or axillary surgery would be associated with a higher false-negative rate and technical failure of SNB. Lymphatic drainage from the lateral and upper portions of the breast to the axilla should be intact after breast reduction surgery or cosmetic breast implants in the submammary or subpectoral position, particularly when the surgery was performed more than 6 to 12 months previously. However, the Panel believes that there are insufficient data at this time and more studies of SNB in this setting are needed before it can be recommended. If SNB is conducted in this setting, it may best be performed with preoperative lymphoscintigraphy (Appendix 2).

Similarly, SNB after axillary surgery has not been widely studied. Although data suggest that SNB may be

attempted in women who have had axillary surgery, the success rate is likely to be lower. In a retrospective analysis, 32 cases of attempted SNB were identified among women with prior axillary surgery. Repeat SNB failed in 25% of such women compared with less than 5% among women who had not had prior axillary surgery.[97] Therefore, the Panel does not recommend SNB in the setting of prior axillary surgery.

Suspicious palpable axillary lymph nodes. Most studies of SNB excluded patients with clinically positive nodes in the axilla. Previous studies have suggested that approximately 25% of clinical axillary examinations yield false-positive findings, and recent experience with SNB supports this observation.[98] Until further data are available, SNB is not recommended in the setting of clinically palpable axillary nodes. If SNB is undertaken in the setting of clinically suspicious nodes, these nodes must be removed regardless of whether they take up dye or radiolabeled colloid.

Preoperative systemic therapy. Several investigators have studied the feasibility of delaying assessment of the axillary lymph nodes in patients who fulfill criteria for SNB until after the completion of preoperative systemic therapy; however, there are some concerns that this strategy may decrease the likelihood of accurate identification of the SLN and increase the chance of a false-negative finding.[99,100] Thus far, a comparison of ALND and SNB after preoperative chemotherapy has not been undertaken in a prospective study. In small institutional case series, the rate of SLN identification has ranged from 85% to 96% and the false-negative rate has ranged from 0% to 33%.[101-107] Data collected at M.D. Anderson Cancer Center between 1994 and 1999 showed that the identification rate improved with experience, whereas the false-negative rate remained stable.[65] The largest study is a retrospective chart review of 2,411 patients with operable breast cancer enrolled in the NSABP B-27 trial of preoperative chemotherapy.[108] Of these patients, 420 (18%) had SNB; at least one SLN was identified in 85% of the 420 patients, and the false-negative rate was 11% for the 340 patients who also had ALND. The loss of pretreatment node staging data to help plan additional postoperative therapy (eg, the extent of radiation fields) has led some to recommend SNB before primary systemic therapy, with ALND performed after chemotherapy if disease is present in the SLN.[109]

In summary, SNB after preoperative systemic chemotherapy is technically feasible. However, because such treatment may eradicate foci of disease in axillary lymph nodes, the long-term clinical significance of negative findings on SNB after preoperative treatment is less clear. This potential loss of prognostic information may complicate clinical decision making for local treatment, such as whether completion axillary dissection is indicated, whether radiation is indicated after mastectomy, or what regions should be irradiated after lumpectomy. If such information would be valuable in planning the local-regional treatment for a given patient, SNB should be considered before systemic therapy is started. The Panel concludes that there are insufficient data to recommend SNB or to suggest appropriate timing of SNB for patients receiving preoperative systemic chemotherapy. The Panel also emphasizes that whether in the preoperative or postoperative setting, a SNB should only be performed in the setting of clinically negative axillary lymph nodes.

What Factors Affect the Success of SNB (including low rates of complications and false-negative findings)?

Summary and recommendations. The ability to evaluate individual or institutional accuracy with SNB on the basis of the proportion of successful mappings and the false-negative rate has enabled the procedure to gain widespread acceptance without prospective randomized trials. As SNB continues to replace ALND for staging of breast cancer, the Panel believes that appropriate training in the procedure and issues of quality control are very important. The strongest predictor of the false-negative rate across trials appears to be the proportion of patients for whom mapping is successful.[24] In addition, the greatest proportion of successful mappings and the lowest false-negative rates were associated with studies in which both blue dye and radiolabeled colloid were used.[24] While the Panel does not believe that ASCO should present separate guidelines for surgeons or institutions about the performance of this procedure, the Panel strongly supports the Guidelines for Performance of Sentinel Lymphadenectomy for Breast Cancer developed and updated in 2003 by the American Society of Breast Surgeons (*http://www.breastsurgeons.org/officialstmts/sentinel.shtml*). The American Society of Breast Surgeons recommends a rate of SLN identification of 85% with a false-negative rate of 5% or less in order to abandon axillary dissection. This Society maintains that performance of a minimum of 20 SNB procedures in combination with axillary dissection or with mentoring is necessary to minimize the risk of false-negative results.[111] The Panel also recommends that surgeons (a) take a formal course on the technique, with didactic and hands-on training components; (b) have an experienced mentor; (c) keep track of individual results, including the proportion of successful mappings, false-negative rates, and complication rates; and (d) maintain follow-up on all patients over time. The Panel believes that these issues are important quality control measures as they could meaningfully impact on false-negative rates. While awaiting further results from RCTs, the Panel believes that high false-negative rates may have a direct adverse impact on patient care including accurate staging, treatment decision making and long-term outcomes including survival. Clearly, the potential for both local as well as systemic undertreatment of patients increases as the false-negative rate increases. Case volume and experience

are clearly important determinants of success, but there are insufficient data to recommend specific volume levels to maintain proficiency. However, the systematic review indicates that the proportion successfully mapped represents the strongest predictor of false-negative rate and may serve as a reasonable quality indicator for this procedure. In addition, the review demonstrates the anticipated reduction in the predictive value of a negative SNB with an increasing lymph node–positive rate in the population studied. Therefore, caution is required when applying the SNB procedure in patients at considerably increased risk for lymph node-positive disease.

Finally, the SNB procedure is very much a team effort with active skilled involvement of multiple disciplines including surgery, pathology, radiology, nuclear medicine, nursing and pharmacy among others. In addition to the individual training and experience required of all team members, optimal results with the SNB requires the integrated and highly coordinated effort that comes with experience and frequent application of the procedure. Importantly, pathologists evaluating SNB specimens should be trained and experienced in the detection of the minimal amount of disease that is characteristically found in SLNs (Appendix 3).

Review of relevant literature. A survey of randomly selected fellows of the American College of Surgeons in 2001 indicated that 77% perform SNB without ALND and 90% use a combination of blue dye and radiolabeled colloid. Of these surgeons, 35% learned to perform the procedure through courses, 31% by observation of colleagues, 26% through a surgical oncology fellowship training program, and 26% by self-instruction. Respondents were directed to indicate all that apply to their situation.[110] Many studies have sought to determine the optimal technique for SNB. Most research has shown that for beginning surgeons, the combinations of radiolabeled colloid, lymphoscintigraphy, and blue dye afford the highest success rates with the lowest false-negative rates.[111-113] A small prospective randomized study in which the use of blue dye alone was compared with a combination of blue dye and radiolabeled colloid showed that surgeons achieved equal results with either technique when initially learning the procedure.[114] Clearly SNB accuracy and the identification rate improve with experience.[112] In one controlled environment, surgeons achieved a 90% rate of SLN identification with a false-negative rate of less than 5% after performing 30 cases. Less success was seen when patients were older than 50 years and when the surgeons had performed 10 or fewer SLN biopsies.[41]

What Are the Potential Benefits and Harms of SNB?

Summary and recommendations. The reported incidence of lymphedema following ALND varies widely and is dependent on many variables, including definition of lymphedema, the extent of surgery, use of radiation therapy, and length of follow-up, among others.[115] SNB is thought to be associated with fewer complications such as infection (cellulitis) of the chest wall and arm, sensory changes, and lymphedema than conventional ALND.[18] The Panel recommends that, as with any medical procedure, written informed consent be obtained from all patients before SNB. The benefits and harms of the procedure, including the potential for a false-negative result should be explained to the patient. Written patient educational materials should provide accurate information on the risk of complications, contraindications for the procedure, the need for a multidisciplinary team (surgeon, nuclear medicine technician, and pathologist), the potential costs (which may be offset by fewer complications and less follow-up care), the lack of long-term survival data, the risk of radiation exposure, and the follow-up protocols for each procedure. A comparison of the data in an understandable format will help to clarify some of the issues for patients making treatment choices.

Review of relevant literature. Several studies clearly show that SNB reduces but does not completely eliminate the risk of lymphedema.[18,115,116] Veronesi et al demonstrated a marked diminution of complications associated with SNB when compared with ALND.[10] A recent RCT similarly found significant reductions in both physical and psychological morbidity, including reductions in postoperative arm swelling, rate of seroma formation, loss of sensitivity to light touch and pinprick, and psychological morbidity.[117] In addition, the two trials reported at recent meetings confirm the expected decreased complication rate of SNB compared with ALND. Early results from a large trial (Axillary Lymphatic Mapping Against Nodal Clearance) in which the morbidity associated with SNB was compared with that associated with conventional ALND were recently presented.[118] Interim analysis at 18 months showed that less lymphedema, shoulder discomfort, sensory deficits, and infections were associated with SNB than with ALND. Quality of life was found to be superior and arm-related morbidity was lower for patients who had SNB. The adverse effects of each procedure diminish markedly over the first 3 months postoperatively, and 5% to 10% of patients who have SNB will describe persistent severe sensory phenomena beyond that time, less than the percentage of women who have the phenomena after ALND.[18]

"Axillary web syndrome," the transient development of tender lymphatic cords along the upper inner arm, is a long-observed but only recently described sequellum to ALND and it appears to occur after SNB as well.[115,119] Allergic reactions to the dye occur in no more than 1% to 2% of patients who have SNB; most of these reactions are hives, which are often strikingly blue and respond to antihistamines. True anaphylactic reactions are rare, occurring in approximately 0.25% to 0.5% of patients.[120] Radiation exposure to the patient, family and friends, surgeon, staff,

and pathologist appears to be small. For mapping with a radiolabeled colloid, an injected dose of technetium (^{99m}Tc) in the range of 0.1 to 1.0 mCi (3.7 to 37 MBq) is approximately 4% of that administered for a conventional bone scan.[121] No isolation, precautions, or special radiation monitoring are required.

There is little in the literature about educational materials for patients and informed consent for SNB for breast cancer.[122,123] More than 4,000 cases of SNB have been reported in the literature, and patients should know that the procedure is widely used and accepted even though it has been compared with ALND in only one recently published RCT.[10] A review of the quality-of-life outcomes commonly seen with each procedure will allow realistic expectations of the outcome of the chosen procedure.[10,123] It should be explained that outcomes improve with greater experience of the surgeon and pathologist, and referrals to qualified teams should be routinely offered. While the quality-of-life advantages to SNB in the short-term may be obvious, the patient should be told that there are limited data from controlled clinical trials in which the two procedures are compared.

Interpretive Summary

The Panel emphasizes that, despite the widespread application of SNB for early-stage breast cancer, it is a relatively new procedure with wide variation in reported test performance characteristics that are dependent on study volume, mapping technique, and the proportion of successful mappings. There are little data on other important clinical outcomes and only one published RCT. The Panel recognizes that SNB is a potentially valuable diagnostic and staging test and believes that studies in which SNB is compared with completion ALND are adequate to determine the diagnostic accuracy of this new procedure. This guideline characterizes the utility of SNB in accurately determining whether axillary metastases are present; related clinical issues of surgical experience, pathologic staging, and appropriate patient selection can provide confidence in a negative SNB result. The range of rates for false-negative findings and SLN identification serve to emphasize the variability and learning curve of this technical procedure in different centers. Nevertheless, once a multidisciplinary team is experienced with the procedure, reasonable levels of accuracy are achieved, with reported identification rates of more than 95%. The Panel considers the findings from SNB as being an acceptably accurate assessment of the axillary status, thus permitting rational treatment decisions for a wide range of patients with early stage breast cancer. The role of routine IHC and/or molecular biologic analysis of the SLN remains unclear. For patients who have a positive SNB and for patients in whom a SLN is not identified intraoperatively, ALND should be considered standard practice until the results of ongoing clinical trials are evaluated. Appropriately identified patients, successfully mapped, with a negative SNB do not require a level I or II ALND. SNB is unlikely to be appropriate for patients who have large tumors, and clinicians should use an individual assessment of particular circumstances before recommending the procedure in these situations. Limitations in understanding the full role of this procedure in the management of women with early-stage breast cancer will not be addressed until the results of ongoing randomized trials are available. Until then, it seems reasonable that SNB be performed by experienced teams at properly equipped centers. Clinicians must continue to use their best judgment for applying and interpreting the results of the SNB based on individual patient and institutional considerations.

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Appendix 1.

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Appendix 2

Lymphoscintigraphic imaging for detection of sentinel lymph nodes. In some medical centers, lymphoscintigraphic imaging using a gamma camera is routinely performed before intraoperative probe detection of radioactivity in sentinel nodes at surgery for axillary staging of breast cancer.[137] Arguments for using imaging instead of simply using a gamma probe over the axilla at the time of surgery include the ability of lymphoscintigraphy to define whether the radiocolloid has drained to the axilla or to other possible sites of drainage, such as the internal mammary, intramammary, contralateralaxillary or supraclavicular nodes.[138-140] In addition, the position of the imaged draining nodes can be marked on the skin at the time of gamma camera imaging, potentially facilitating the detection of sentinel nodes at the time of surgery with a gamma probe. Frequency of visualization of axillary sentinel nodes is typically in the 60% to 90% range in most centers, with more recent studies typically in the higher part of this range.[141-143] There is considerable variability in the type of radiocolloid used in different parts of the world. Using very small particles may result in a higher frequency of visualization of nodes, but this is somewhat controversial, as some studies have suggested larger colloids are preferable. Clearly, many colloidal preparations can be effective in lymphoscintigraphy, and in the United States both unfiltered and filtered ^{99m}Tc sulfur colloid agents are normally used.[137,141,144] An area of some controversy is whether injections for lymphoscintigraphic imaging should only be perilesional, or whether injections in the subdermal skin overlying the tumor, or in the periareolar area, are most appropriate.[142,145] A concern with perilesional injections only is that there appears to be a significantly higher frequency of nonvisualization of sentinel nodes versus injections in the skin or periareolar region.[137,142,145] In some centers, injections in more than one area of the breast are given, peritumoral and periareolar, for example.[141,145] Obese and elderly patients tend to have a higher frequency of false-negative lymphoscintigraphy than thinner, younger patients in some series.[142] In addition, imaging done soon after injection (eg, $<$ 2 hours) will generally detect fewer positive lymph nodes than imaging done 6 to 18 hours after injection. If later imaging, which can be performed by injections the afternoon before the surgery is planned, is performed, adequate doses of ^{99m}Tc colloid must be given, typically at least 10 mBq and often more.[141-143] In general, delayed imaging detects more nodes than does early imaging.

There is substantial variability in the frequency of imaging visualization of internal mammary nodes, ranging from under 10% to nearly 40% in some series. It is clear that although medial breast cancers are more likely to drain to internal mammary nodes than laterally situated tumors, there can be drainage to internal mammary nodes from tumors located in almost any location in the breast tissue.[140,141] The frequency of internal mammary nodal visualization may be dependent on the type of colloid used and route of injection as well as the time from imaging until injection. In most series, the use of an intraoperative gamma probe system is more sensitive than use of the gamma camera for detecting axillary sentinel nodes (ie, more sentinel nodes are identified with the probe than by imaging), as there are substantial geometric and physical considerations favoring high sensitivity when a detector is placed immediately over a focus of radioactivity, rather than imaging with a gamma camera from a distance

through a great deal of body tissue.[137,141] Given the lower sensitivity of the gamma camera for detection of nodes, longer periods of time from injection until imaging are often used than in studies using a gamma probe alone and some imaging protocols involve injection the afternoon before planned surgery. Even if no lymph nodes are visualized on lymphoscintigraphy, probe-based detection of sentinel nodes should be performed as sentinel nodes can be found in the majority of cases even when negative on external gamma camera imaging. While data are limited, nonvisualization with a gamma camera and nondetection of sentinel nodes by probe is a situation associated with a relatively higher frequency of tumor involvement in lymph nodes and axillary dissection may be indicated in such cases.[140,142,143,146] Small handheld gamma cameras, which provide an image rather than probe counts, may provide unique advantages over probe detectors alone, but are not yet in widespread use.[147]

Thus, lymphoscintigraphic imaging can be useful in demonstrating unexpected draining nodes, especially in the internal mammary region and may guide probe-based surgery. The clinical significance of such findings may include additional invasive procedures to determine the nodal histology or the use of external-beam irradiation of internal mammary nodes—depending on the therapeutic intent. It is clear that lymphoscintigraphy is not a substitute for probe-based surgery but is adjunctive. Lymphoscintigraphy is, however, a routine part of the practice pattern in many centers where it precedes and can direct the performance of the radionuclide guided probe-based sentinel node surgery.

Appendix 3

Pathologic Evaluation of Sentinel Lymph Nodes

Introduction. Sentinel node procedures are increasingly used in the management and staging of various malignant diseases, including breast cancer.[124] For the approach to be effective, surgeons must identify and remove all true SLNs and pathologists must carefully and systematically examine them. Clinicians, pathologists, and patients should be aware of the significance of identifying metastases in lymph nodes, as well as the possibility that small metastases may be missed. Accurate identification of node metastases is the firm basis on which appropriate treatment decisions are made.[125] Pathologists, as part of their standard analysis, must quantify tumor burden in the nodes. This assessment will be increasingly important as SLN-derived information becomes better understood. Consistent categoric reporting, using the American Joint Commission on Cancer (AJCC)/International Union Against Cancer (UICC) staging system, facilitates uniform communication with clinicians and, as national databases mature, analysis of outcomes.

Management of the gross specimen. Pathologists receive either single lymph nodes dissected free of fat or axillary fat containing one or more lymph nodes. Fatty nodules are carefully dissected to identify all lymph nodes. Lymph nodes are inspected for blue color, measured, and cut into sections no thicker than 2.0 mm through and parallel to the longest meridian. Each SLN is submitted in a separate cassette or identified by colored ink to permit accurate assessment of the total number of lymph nodes and number of involved lymph nodes; all node sections are submitted for microscopic examination. Because of the short half-life and limited penetration of technetium, health risks to those handling SLNs are negligible.[126]

Intraoperative assessment of SLNs. Intraoperative assessment of SLNs was used in the development of the modern SNB technique.[12] It allows immediate axillary dissection when metastasis is found in the SLN. An understanding of the strengths and limitations of intraoperative examination of SLNs is critical. Approximately 75% of patients considered for SNB have tumor-free lymph nodes in permanent sections. In the 25% of patients with positive nodes, disease will not be detected intraoperatively because of sampling limitations and the challenge of detecting micrometastases. For every 100 patients who have SLNs evaluated intraoperatively, 16 to 17 will have positive nodes and 8 to 9 will have false-negative results. Each institution must establish a policy on intraoperative assessment or deferral to permanent sections. Both approaches are legitimate, provided that patients are informed of the possibility and risks of a second surgery for completion axillary dissection. Intraoperative assessment may be by gross inspection, imprint cytology, evaluation of cells scraped from the cut surface of the node, or frozen section. SLNs that are positive on gross examination are most likely to be associated with positive nonsentinel nodes. It is therefore of real value to identify this category of SLNs early in surgical management. Immediate cytologic evaluation or frozen section can confirm suspicious gross appearances. Cut surfaces of SLNs touched to glass slides provide cellular imprints and cell-rich scrapes of the SLN surfaces may be smeared onto a slide. A positive imprint/smear is of immediate practical assistance, but negative imprints/smears are not definitive evidence that a node is tumor free. Suspicious findings should be reported as not diagnostic for tumor and deferred to paraffin section. Intraoperative frozen sections carry the risk of significant destruction of potentially diagnostic tissue. However, with experienced clinicians, frozen section may be the most desirable intraoperative assessment for some surgeon/pathologist teams, providing slightly higher sensitivity for detection of metastases than immediate cytology alone.[127] The quality of frozen tissue preparations is seldom as good as those prepared from well-fixed tissue, and incomplete sections may exclude the critical subcapsular sinus. Prior freezing may compromise the quality of paraffin section histology.

Sampling SLNs. Most SLNs with macrometastases or micrometastases are readily identified by examination of

H&E-stained sections, an approach endorsed by leading pathology organizations.[128,129] Limited step sections from the block (top level plus one or two sections cut at 200- to 500-μm intervals into the block) enhance detection of micrometastases by allowing evaluation of more of the subcapsular sinus, the location in which micrometastases are most often found. Superficial serial sections limit sampling to the upper levels of the block. If the SLN has been grossly sectioned as recommended, virtually all macrometastases ($>$ 2.0 mm) and most micrometastases ($>$ 0.2 mm to 2.0 mm) will be detected on limited H&E-stained step sections.[130-132] In some patients, isolated tumor cells and clusters ($\leq$ 0.2 mm) will also be detected with use of this sectioning technique, particularly if immunohistochemical analysis (IHC) is utilized.

IHC analysis. IHC analysis may facilitate screening of SLN sections, but the significance and practical relevance of small clusters of breast cancer cells detected by this method are debated. The use of antibodies to cytokeratin is of value in lobular carcinoma, where tumor cells may be extensive and closely resemble lymphoid cells. Antibodies to cytokeratins often disclose small numbers of tumor cells not readily visible on H&E-stained sections.[42,133] The biologic relevance of small numbers of tumor cells is unknown, and it is hoped that the relevance will be determined by careful analysis of results from ongoing clinical trials. Another guideline panel has recommended against the use of routine IHC screening[134,135] The decision to utilize IHC analysis and act on the results remains for now a matter of discussion among individual surgeons, oncologists, and pathologists, based on a determination of the best course for their patients, assessed from their own experience and review of the available literature. If IHC analysis is to be performed, patients should be informed of the uncertain significance of any positive results. Regardless of the institutional decision on utilization of IHC analysis, the pathologic findings should be reported in accordance with AJCC/UICC guidelines.

Pathology reporting of SLNs. Pathologists must provide sufficient information in their pathology reports to facilitate accurate cancer staging using the criteria of the current AJCC/UICC system.[44] This information includes documentation of tumor burden in the nodes. If any node metastasis is larger than 2.0 mm, the total number of tumor-positive nodes determines the N category. Special rules apply if internal mammary, supraclavicular, or infraclavicular nodes contain tumor. Micrometastases now have an upper and lower size limit and are individual tumor deposits larger than 0.2 mm but not larger than 2.0 mm. The lower limit accommodates the frequency of small tumor deposit identified in SLNs. When the largest confluent focus of node tumor is no larger than 0.2 mm, regardless of the method of detection, deposits are referred to as "isolated tumor cells or tumor cell clusters (ITC)." Micrometastases are classified as pN1mi. Isolated tumor cells or cell clusters are classified pN0 (i+). A recent modification of the staging guidelines extends the use of the (i+) modifier beyond detection by IHC analysis to any metastasis of 0.2 mm or less, regardless of the method of detection.[136] Careful attention must be given to accurately reporting the correct number of tumor-positive nodes. Bisected, trisected, or serially sectioned positive SLNs may be over-recorded without coordination between the dissector of the gross specimen and the attending pathologist. This underscores the need to separately identify SLNs and carefully document the manner in which they are sectioned before microscopic examination.

Molecular biology. Sophisticated molecular biology approaches such as the reverse transcriptase polymerase chain reaction are under active investigation for their potential applicability to evaluation of SLNs. These approaches are highly sensitive and, if required, permit the evaluation of relatively large amounts of tissue. However, during preparations for analysis, the tissues are destroyed and it is therefore not possible to determine the cell from which an augmented signal for tumor marker mRNA originates. For this reason, it is likely that such approaches will be used in parallel with histologic evaluation. For the present, such techniques should be evaluated within controlled studies and are not ready to be applied in routine management.

Pathology Summary Recommendations. All true SLNs and incidental nonsentinel nodes require special attention.

1. All submitted nodes should be counted and measured, with notations on the coloration and the relative radioactive uptake reported by the surgeon.

2. Intraoperative evaluation of sentinel nodes may involve inspection of cut faces of the node, cytology of node imprints, or cell smears or frozen sections. Evaluation of the SLN is likely to be more accurate on the basis of paraffin sections.

3. Nodes are to be cut into perimeridianal (longitudinal) slices no thicker than 2 mm. At a minimum, full cross-sections of each SLN slice should be prepared and examined with H&E staining. Additional micrometastases are more likely to be detected with step sections at 200- to 500-μm intervals than with superficial serial sections alone.

4. IHC analysis with antibodies to cytokeratins facilitates the detection of small tumor deposits. There is insufficient evidence at present to recommend that IHC to cytokeratin be performed routinely. Routine IHC is not currently recommended for the evaluation of sentinel nodes from patients with breast cancer.

5. Reports should indicate the category of metastasis identified and the patterns (single cells or clusters, micrometastases, macrometastases, and so on) of tumor present using current AJCC/UICC criteria. The maximal size of the largest tumor cell cluster should be recorded.

6. Molecular approaches remain investigational, and tissue potentially required for histologic diagnosis should not be utilized for investigational purposes until the diagnosis is secure.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

1. Rivadeneira DE, Simmons RM, Christos PJ, et al: Predictive factors associated with axillary lymph node metastases in T1a and T1b breast carcinomas: Analysis in more than 900 patients. J Am Coll Surg 191:1-8, 2000

2. Gann PH, Colilla SA, Gapstur SM, et al: Factors associated with axillary lymph node metastasis from breast carcinoma: Descriptive and predictive analyses. Cancer 86:1511-1519, 1999

3. Tabar L, Chen HH, Duffy SW, et al: A novel method for prediction of long-term outcome of women with T1a, T1b, and 10-14 mm invasive breast cancers: A prospective study. [erratum appears in Lancet 355:1372, 2000]. Lancet 355:429-433, 2000

4. Gajdos C, Tartter PI, Bleiweiss IJ: Lymphatic invasion, tumor size, and age are independent predictors of axillary lymph node metastases in women with T1 breast cancers. Ann Surg 230: 692-696, 1999

5. Olivotto IA, Jackson JS, Mates D, et al: Prediction of axillary lymph node involvement of women with invasive breast carcinoma: A multivariate analysis. Cancer 83:948-955, 1998

6. Fein DA, Fowble BL, Hanlon AL, et al: Identification of women with T1-T2 breast cancer at low risk of positive axillary nodes. J Surg Oncol 65:34-39, 1997

7. Giuliano AE, Jones RC, Brennan M, et al: Sentinel lymphadenectomy in breast cancer. J Clin Oncol 15:2345-2350, 1997

8. Cady B, Stone MD, Schuler JG, et al: The new era in breast cancer: Invasion, size, and nodal involvement dramatically decreasing as a result of mammographic screening. Arch Surg 131:301-308, 1996

9. Haffty BG, Ward B, Pathare P, et al: Reappraisal of the role of axillary lymph node dissection in the conservative treatment of breast cancer. J Clin Oncol 15:691-700, 1997

10. Veronesi U, Paganelli G, Viale G, et al: A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 349:546-553, 2003

11. Morton DL, Thompson JF, Essner R, et al: Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: A multicenter trial—Multicenter Selective Lymphadenectomy Trial Group. Ann Surg 230:453-465, 1999

12. Morton DL, Wen DR, Wong JH, et al: Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 127:392-399, 1992

13. Thompson JF, McCarthy WH, Bosch CM, et al: Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. Melanoma Res 5:255-260, 1995

14. Reintgen D, Cruse CW, Wells K, et al: The orderly progression of melanoma nodal metastases. Ann Surg 220:759-767, 1994

15. Giuliano AE, Haigh PI, Brennan MB, et al: Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer.[erratum appears in J Clin Oncol 18:3877, 2000]. J Clin Oncol 18:2553-2559, 2000

16. Schrenk P, Rieger R, Shamiyeh A, et al: Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer 88:608-614, 2000

17. Burak WE, Hollenbeck ST, Zervos EE, et al: Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. Am J Surg 183:23-27, 2002

18. Temple LK, Baron R, Cody HS 3rd, et al: Sensory morbidity after sentinel lymph node biopsy and axillary dissection: A prospective study of 233 women. Ann Surg Oncol 9:654-662, 2002

19. Haid A, Kuehn T, Konstantiniuk P, et al: Shoulder-arm morbidity following axillary dissection and sentinel node only biopsy for breast cancer. Eur J Surg Oncol 28:705-710, 2002

20. Swenson KK, Nissen MJ, Ceronsky C, et al: Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer. Ann Surg Oncol 9:745-753, 2002

21. Golshan M, Martin WJ, Dowlatshahi K: Sentinel lymph node biopsy lowers the rate of lymphedema when compared with standard axillary lymph node dissection. Am Surg 69:209-212, 2003

22. Schijven MP, Vingerhoets AJ, Rutten HJ, et al: Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. Eur J Surg Oncol 29:341-350, 2003

23. Edge SB, Niland JC, Bookman MA, et al: Emergence of sentinel node biopsy in breast cancer as standard-of-care in academic comprehensive cancer centers. J Natl Cancer Inst 95: 1514-1521, 2003

24. Kim T, Agboola O, Giuliano A, et al: Lymphatic mapping and sentinel lymph node sampling in early-stage breast cancer: A Meta-analysis. Cancer (in press)

25. Cox CE, Bass SS, McCann CR, et al: Lymphatic mapping and sentinel lymph node biopsy in patients with breast cancer. Annu Rev Med 51:525-542, 2000

26. Fraile M, Rull M, Julian FJ, et al: Sentinel node biopsy as a practical alternative to axillary lymph node dissection in breast cancer patients: An approach to its validity.[erratum appears in Ann Oncol 11:1619, 2000]. Ann Oncol 11:701-705, 2000

27. Lyman GH, Kim TY, Giuliano AE: A systematic review and meta-analysis of lymphatic mapping and sentinel node biopsy (SNB) in early-stage breast cancer (ESBC). Breast Cancer Res Treat 88:S77, 2004 (suppl 1)

28. Institute for Clinical Systems Improvement: Lymphatic mapping with sentinel node biopsy for breast cancer. 2002, pp 1-20

29. Tafra L, Lannin DR, Swanson MS, et al: Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. Ann Surg 233:51-59, 2001

30. Schwartz GF, Giuliano AE, Veronesi U, et al: Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19-22, 2001, Philadelphia, Pennsylvania. Cancer 94:2542-2551, 2002

31. Cantin J, Scarth H, Levine M, et al: Clinical practice guidelines for the care and treatment of breast cancer, 13: Sentinel lymph node biopsy.[erratum appears in CMAJ 165:744, 2001]. CMAJ 165:166-173, 2001

32. Kuehn T, Vogl FD, Helms G, et al: Sentinel-node biopsy for axillary staging in breast cancer: Results from a large prospective German

multi-institutional trial. Eur J Surg Oncol 30:252-259, 2004

33. Naik AM, Fey J, Gemignani M, et al: The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: A follow-up study of 4008 procedures. Ann Surg 240:462-471, 2004

34. Cody HS 3rd, Fey J, Akhurst T, et al: Complementarity of blue dye and isotope in sentinel node localization for breast cancer: Univariate and multivariate analysis of 966 procedures.. Ann Surg Oncol 8:13-19, 2001

35. Wong SL, Edwards MJ, Chao C, et al: The effect of prior breast biopsy method and concurrent definitive breast procedure on success and accuracy of sentinel lymph node biopsy. Ann Surg Oncol 9:272-277, 2002

36. Hill AD, Tran KN, Akhurst T, et al: Lessons learned from 500 cases of lymphatic mapping for breast cancer. Ann Surg 229:528-535, 1999

37. Martin RC, Derossis AM, Fey J, et al: Intradermal isotope injection is superior to intramammary in sentinel node biopsy for breast cancer. Surgery 130:432-438, 2001

38. Juian TB, Krag D, Brown A, et al: A randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients. Breast Cancer Res Treat, 2004 (suppl 19; abstr 140)

39. Hansen NM, Grube BJ, Giuliano AE: Clinical significance of axillary micrometastases in breast cancer: How small is too small. Proc Am Soc Clin Oncol 20:20A, 2001 (abstr 91)

40. Cox CE, Salud CJ, Cantor A, et al: Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. J Am Coll Surg 193:593-600, 2001

41. de Mascarel I, Bonichon F, Coindre JM, et al: Prognostic significance of breast cancer axillary lymph node micrometastases assessed by two special techniques: Reevaluation with longer follow-up. Br J Cancer 66:523-527, 1992

42. Turner RR, Ollila DW, Stern S, et al: Optimal histopathologic examination of the sentinel lymph node for breast carcinoma staging. Am J Surg Pathol 23:263-267, 1999

43. Singletary SE, Allred C, Ashley P, et al: Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 20:3628-3636, 2002

44. Green FL, Page DL, Fleming ID, et al: AJCC Cancer Staging Manual (ed 6). New York, NY, Springer, 2002

45. McCready DR, Yong WS, Ng AK, et al: Influence of the new AJCC breast cancer staging system on sentinel lymph node positivity and false-negative rates. J Natl Cancer Inst 96:873-875, 2004

46. Fisher B, Redmond C, Fisher ER, et al: Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 312:674-681, 1985

47. Galper S, Recht A, Silver B, et al: Is radiation alone adequate treatment to the axilla for patients with limited axillary surgery? Implications for treatment after a positive sentinel node biopsy. Int J Radiat Oncol Biol Phys 48:125-132, 2000

48. Turner RR, Chu KU, Qi K, et al: Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. Cancer 89:574-581, 2000

49. Weiser MR, Montgomery LL, Tan LK, et al: Lymphovascular invasion enhances the prediction of non-sentinel node metastases in breast cancer patients with positive sentinel nodes. Ann Surg Oncol 8:145-149, 2001

50. Kamath VJ, Giuliano R, Dauway EL, et al: Characteristics of the sentinel lymph node in breast cancer predict further involvement of higher-echelon nodes in the axilla: A study to evaluate the need for complete axillary lymph node dissection. Arch Surg 136:688-692, 2001

51. Rahusen FD, Torrenga H, van Diest PJ, et al: Predictive factors for metastatic involvement of nonsentinel nodes in patients with breast cancer. Arch Surg 136:1059-1063, 2001

52. Wong SL, Edwards MJ, Chao C, et al: Predicting the status of the nonsentinel axillary nodes: A multicenter study. Arch Surg 136:563-568, 2001

53. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al: A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy.[see comment]. Ann Surg Oncol 10:1140-1151, 2003

54. Nasser IA, Lee AK, Bosari S, et al: Occult axillary lymph node metastases in "node-negative" breast carcinoma. Hum Pathol 24:950-957, 1993

55. Pickren J: Significance of occult metastases: A study of breast cancer. Cancer 14:1266-1271, 1961

56. Rosen PP, Saigo PE, Braun DW Jr., et al: Occult axillary lymph node metastases from breast cancers with intramammary lymphatic tumor emboli. Am J Surg Pathol 6:639-641, 1982

57. Fisher ER, Swamidoss S, Lee CH, et al: Detection and significance of occult axillary node metastases in patients with invasive breast cancer. Cancer 42:2025-2031, 1978

58. Trojani M, de Mascarel I, Bonichon F, et al: Micrometastases to axillary lymph nodes from carcinoma of breast: Detection by immunohistochemistry and prognostic significance. Br J Cancer 55:303-306, 1987

59. Hainsworth PJ, Tjandra JJ, Stillwell RG, et al: Detection and significance of occult metastases in node-negative breast cancer. Br J Surg 80:459-463, 1993

60. McGuckin MA, Cummings MC, Walsh MD, et al: Occult axillary node metastases in breast cancer: Their detection and prognostic significance. Br J Cancer 73:88-95, 1996

61. Cote RJ, Peterson HF, Chaiwun B, et al: Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. International Breast Cancer Study Group. Lancet 354:896-900, 1999

62. Sarvi M, Mehta P, Vallow L, et al: Is nodal irradiation necessary in breast cancer patients with positive sentinel node biopsy without axillary dissection. Int J Radiat Oncol Biol Phys 54:232-233, 2002 (suppl 1; abstr 2038)

63. Fant JS, Grant MD, Knox SM, et al: Preliminary outcome analysis in patients with breast cancer and a positive sentinel lymph node who declined axillary dissection. Ann Surg Oncol 10:126-130, 2003

64. Guenther JM, Hansen NM, DiFronzo LA, et al: Axillary dissection is not required for all patients with breast cancer and positive sentinel nodes. Arch Surg 138:52-56, 2003

65. Stearns V, Ewing CA, Slack R, et al: Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliably represent the axilla except for inflammatory breast cancer. Ann Surg Oncol 9:235-242, 2002

66. Krag DN, Weaver DL, Alex JC, et al: Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 2:335-340, 1993

67. Giuliano AE, Kirgan DM, Guenther JM, et al: Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 220:391-401, 1994

68. Veronesi U, Paganelli G, Viale G, et al: Sentinel lymph node biopsy and axillary dissection in breast cancer: Results in a large series. J Natl Cancer Inst 91:368-373, 1999

69. McMasters KM, Wong SL, Martin RC 2nd, et al: Dermal injection of radioactive colloid is superior to peritumoral injection for breast cancer sentinel lymph node biopsy: Results of a multiinstitutional study. Ann Surg 233:676-687, 2001

70. Kern KA: Concordance and validation study of sentinel lymph node biopsy for breast cancer using subareolar injection of blue dye and technetium 99m sulfur colloid. J Am Coll Surg 195:467-475, 2002

71. Klimberg VS, Rubio IT, Henry R, et al: Subareolar versus peritumoral injection for location of the sentinel lymph node. Ann Surg 229: 860-865, 1999

72. Kumar R, Jana S, Heiba SI, et al: Retrospective analysis of sentinel node localization in multifocal, multicentric, palpable, or nonpalpable breast cancer. J Nucl Med 44:7-10, 2003

73. Schrenk P, Wayand W: Sentinel-node biopsy in axillary lymph-node staging for patients with multicentric breast cancer. Lancet 357:122, 2001

74. Tousimis E, Van Zee KJ, Fey JV, et al: The accuracy of sentinel lymph node biopsy in multcentric and multifocal invasive breast cancer. J Am Coll Surg 197:529-535, 2003

75. Cox CE, Dupont E, Whitehead GF, et al: Age and body mass index may increase the chance of failure in sentinel lymph node biopsy for women with breast cancer. Breast J 8:88-91, 2002

76. Jemal A, Murray T, Samuels A, et al: Cancer statistics, 2003. CA Cancer J Clin 53:5-26, 2003

77. Borgen PI, Wong GY, Vlamis V, et al: Current management of male breast cancer: A review of 104 cases. Ann Surg 215:451-459, 1992

78. Jepson AS, Fentiman IS: Male breast cancer. Int J Clin Pract 52:571-576, 1998

79. Spence RA, MacKenzie G, Anderson JR, et al: Long-term survival following cancer of the male breast in Northern Ireland: A report of 81 cases. Cancer 55:648-652, 1985

80. Erlichman C, Murphy KC, Elhakim T: Male breast cancer: A 13-year review of 89 patients. J Clin Oncol 2:903-909, 1984

81. Cutuli B, Lacroze M, Dilhuydy JM, et al: Male breast cancer: Results of the treatments and prognostic factors in 397 cases. Eur J Cancer 31A:1960-1964, 1995

82. Mullan MH, Kissin MW: Positive sentinel node biopsy in male breast carcinoma. ANZ Journal of Surgery 71:438-440, 2001

83. Hill AD, Borgen PI, Cody HS III: Sentinel node biopsy in male breast cancer. Eur J Surg Oncol 25:442-443, 1999

84. Gennari R, Renne G, Travaini L, et al: Sentinel node biopsy in male breast cancer: Future standard treatment? Eur J Surg 167:461-462, 2001

85. Port ER, Fey JV, Cody HS III, et al: Sentinel lymph node biopsy in patients with male breast carcinoma. Cancer 91:319-323, 2001

86. Albo D, Ames FC, Hunt KK, et al: Evaluation of lymph node status in male breast cancer patients: A role for sentinel lymph node biopsy. Breast Cancer Res Treat 77:9-14, 2003

87. Gentilini O, Cremonesi M, Trifirò G, et al: Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 15:1348-1351, 2004

88. Veronesi U, Marubini E, Mariani L, et al: The dissection of internal mammary nodes does not improve the survival of breast cancer patients: 30-year results of a randomised trial. Eur J Cancer 35:1320-1325, 1999

89. Veronesi U, Cascinelli N, Bufalino R, et al: Risk of internal mammary lymph node metastases and its relevance on prognosis of breast cancer patients. Ann Surg 198:681-684, 1983

90. Veronesi U, Cascinelli N, Greco M, et al: Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. Ann Surg 202:702-707, 1985

91. Klauber-DeMore N, Bevilacqua JL, Van Zee KJ, et al: Comprehensive review of the management of internal mammary lymph node metastases in breast cancer. J Am Coll Surg 193:547-555, 2001

92. Klauber-DeMore N, Tan LK, Liberman L, et al: Sentinel lymph node biopsy: Is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? Ann Surg Oncol 7:636-642, 2000

93. Cody HS, Klauber-Demore N, Borgen PI, et al: Is it really duct carcinoma in situ? Ann Surg Oncol 8:617-619, 2001

94. Albertini JJ, Lyman GH, Cox C, et al: Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 276:1818-1822, 1996

95. Krag D, Weaver D, Ashikaga T, et al: The sentinel node in breast cancer: A multicenter validation study. N Engl J Med 339:941-946, 1998

96. Haigh PI, Hansen NM, Qi K, et al: Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer. Ann Surg Oncol 7:21-27, 2000

97. Port ER, Fey J, Gemignani ML, et al: Reoperative sentinel lymph node biopsy: A new option for patients with primary or locally recurrent breast carcinoma. J Am Coll Surg 195:167-172, 2002

98. Fisher B, Wolmark N, Bauer M, et al: The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet 152:765-772, 1981

99. Newman LA, Pernick NL, Adsay V, et al: Histopathologic evidence of tumor regression in the axillary lymph nodes of patients treated with preoperative chemotherapy correlates with breast cancer outcome.[erratum appears in Ann Surg Oncol 11:350]. Ann Surg Oncol 10:734-739, 2003

100. Buchholz TA, Hunt KK, Whitman GJ, et al: Neoadjuvant chemotherapy for breast carcinoma: Multidisciplinary considerations of benefits and risks. Cancer 98:1150-1160, 2003

101. Miller AR, Thomason VE, Yeh IT, et al: Analysis of sentinel lymph node mapping with immediate pathologic review in patients receiving preoperative chemotherapy for breast carcinoma. Ann Surg Oncol 9:243-247, 2002

102. Nason KS, Anderson BO, Byrd DR, et al: Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. Cancer 89:2187-2194, 2000

103. Tafra L, Verbanac KM, Lannin DR: Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. Am J Surg 182:312-315, 2001

104. Julian TB, Patel N, Dusi D, et al: Sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer. Am J Surg 182:407-410, 2001

105. Haid A, Tausch C, Lang A, et al: Is sentinel lymph node biopsy reliable and indicated after preoperative chemotherapy in patients with breast carcinoma? Cancer 92:1080-1084, 2001

106. Fernandez A, Cortes M, Benito E, et al: Gamma probe sentinel node localization and biopsy in breast cancer patients treated with a neoadjuvant chemotherapy scheme. Nucl Med Commun 22:361-366, 2001

107. Balch GC, Mithani SK, Richards KR, et al: Lymphatic mapping and sentinel lymphadenectomy after preoperative therapy for stage II and III breast cancer. Ann Surg Oncol 10:616-621, 2003

108. Mamounas EP, Brown A, Smith R, et al: Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: Updated results from NSABP B-27. Proc Am Soc Clin Oncol, 2002 (abstr 140)

109. Sabel MS, Schott AF, Kleer CG, et al: Sentinel node biopsy prior to neoadjuvant chemotherapy. Am J Surg 186:102-105, 2003

110. Lucci A Jr., Kelemen PR, Miller C 3rd, et al: National practice patterns of sentinel lymph node dissection for breast carcinoma. J Am Coll Surg 192:453-458, 2001

111. McMasters KM, Tuttle TM, Carlson DJ, 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 18:2560-2566, 2000

112. McMasters KM, Wong SL, Chao C, et al: Defining the optimal surgeon experience for breast cancer sentinel lymph node biopsy: A model for implementation of new surgical techniques. Ann Surg 234:292-300, 2001

113. Derossis AM, Fey J, Yeung H, et al: A trend analysis of the relative value of blue dye and isotope localization in 2,000 consecutive cases of sentinel node biopsy for breast cancer. J Am Coll Surg 193:473-478, 2001

114. Morrow M, Rademaker AW, Bethke KP, et al: Learning sentinel node biopsy: Results of a prospective randomized trial of two techniques. Surgery 126:714-722, 1999

115. Erickson VS, Pearson ML, Ganz PA, et al: Arm edema in breast cancer patients. J Natl Cancer Inst 93:96-111, 2001

116. Sener SF, Winchester DJ, Martz CH, et al: Lymphedema after sentinel lymphadenectomy for breast carcinoma. Cancer 92:748-752, 2001

117. Purushotham AD, Upponi S, Klevesath MB, et al: Morbidity after sentinel lymph node biopsy in primary breast cancer: Results from a randomized controlled trial. J Clin Oncol 23:4312-4321, 2005

118. Fallowfield LJ, Jenkins VA, Johnson L, et al: Impact of sentinel node biopsy on quality of life in the ALMANAC trial. Breast Cancer Res Treat 88:S77, 2004 (suppl 1)

119. Moskovitz AH, Anderson BO, Yeung RS, et al: Axillary web syndrome after axillary dissection. Am J Surg 181:434-439, 2001

120. Montgomery LL, Thorne AC, Van Zee KJ, et al: Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. Anesth Analg 95:385-388, 2002

121. Waddington WA, Keshtgar MR, Taylor I, et al: Radiation safety of the sentinel lymph node technique in breast cancer. Eur J Nucl Med 27:377-391, 2000

122. Swenson KK, Sladek ML, Lally RM, et al: Educating patients on sentinel lymph node dissection for breast cancer. Cancer Practice 9:92-96, 2001

123. Peintinger F, Reitsamer R, Stranzl H, et al: Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. Br J Cancer 89:648-652, 2003

124. Cochran AJ, Roberts AA, Saida T: The place of lymphatic mapping and sentinel node biopsy in oncology. Int J Clin Oncol 8:139-150, 2003

125. Cochran AJ: Sentinel lymph node pathology, in Kirkham N, Lemoine NR (eds): Progress in Pathology, Vol 5. Cambridge, UK, Cambridge University Press, 2001, p 208

126. Fitzgibbons PL, LiVolsi VA: Recommendations for handling radioactive specimens obtained by sentinel lymphadenectomy: Surgical Pathology Committee of the College of American Pathologists, and the Association of Directors of Anatomic and Surgical Pathology. Am J Surg Pathol 24:1549-1551, 2000

127. Van Diest PJ, Torrenga H, Borgstein PJ, et al: Reliability of intraoperative frozen section and imprint cytological investigation of sentinel lymph nodes in breast cancer. Histopathology 35:14-18, 1999

128. Fitzgibbons PL, Page DL, Weaver D, et al: Prognostic factors in breast cancer: College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 124:966-978, 2000

129. Association of Directors of Anatomic and Surgical Pathology: Recommendations for processing and reporting of lymph node specimens submitted for evaluation of metastatic disease. Am J Clin Pathol 115:799-801, 2001

130. Viale G, Bosari S, Mazzarol G, et al: Intraoperative examination of axillary sentinel lymph nodes in breast carcinoma patients. Cancer 85: 2433-2438, 1999

131. Turner RR: Histopathologic processing of the sentinel lymph node. Semin Breast Dis 5:35-40, 2002

132. Weaver DL, Krag DN, Ashikaga T, et al: Pathologic analysis of sentinel and nonsentinel lymph nodes in breast carcinoma: A multicenter study. Cancer 88:1099-1107, 2000

133. Wells CA, Heryet A, Brochier J, et al: The immunocytochemical detection of axillary micrometastases in breast cancer. Br J Cancer 50:193-197, 1984

134. National Comprehensive Cancer Network: The NCCN Breast Cancer Clinical Practice Guidelines in Oncology, version 2.2005. Accessed August 6, 2005. Available at http://www.nccn.org

135. College of American Pathologists. www.cap.org

136. Singletary SE, Greene FL, Sobin LH: Classification of isolated tumor cells: Clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. Cancer 98:2740-2741, 2003

137. Alazraki NP, Styblo T, Grant SF, et al: Sentinel node staging of early breast cancer using lymphoscintigraphy and the intraoperative gamma detecting probe. Radiol Clin North Am 39:947-956, 2001

138. Dupont EL, Salud CJ, Peltz ES, et al: Clinical relevance of internal mammary node mapping as a guide to radiation therapy. Am J Surg 182:321-324, 2001

139. Benamor M, Nos C, Freneaux P, et al: Impact of internal mammary sentinel node imaging in breast cancer. Clin Nucl Med 28:375-378, 2003

140. Carcoforo P, Basaglia E, Soliani G, et al: Sentinel node biopsy in the evaluation of the internal mammary node chain in patients with breast cancer. Tumori 88:S5-S7, 2002

141. Uren RF, Howman-Giles R, Chung D, et al: Nuclear medicine aspects of melanoma and breast lymphatic mapping. Semin Oncol 31:338-348, 2004

142. Chakera AH, Friis E, Hesse U, et al: Factors of importance for scintigraphic nonvisualization of sentinel nodes in breast cancer. Eur J Nucl Med Mol Imaging 32:286-293, 2005

143. Tanis PJ, van Sandick JW, Nieweg OE, et al: The hidden sentinel node in breast cancer. Eur J Nucl Med Mol Imaging 29:305-311, 2002

144. Linehan DC, Hill AD, Tran KN, et al: Third sentinel lymph node biopsy in breast cancer: Ufiltered radioisotope is superior to filtered. J Am Coll Surg 188:377-381,1999

145. Kern KA, Rosenberg RJ: Preoperative lymphoscintigraphy during lymphatic mapping for breast cancer: Improved sentinel node imaging using subareolar injection of technetium 99m sulfur colloid. J Am Coll Surg 191:479-489, 2000

146. Johnson N, Soot L, Nelson J, et al: Sentinel node biopsy and internal mammary lymphatic mapping in breast cancer Am J Surg 179:386-388, 2000

147. Motomura K, Noguchi A, Hashizume T, et al: Usefulness of a solid-state gamma camera for sentinel node identification in patients with breast cancer. J Surg Oncol 1:12-17, 2005