

Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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ABSTRACT

Purpose

To provide evidence-based recommendations to practicing oncologists, surgeons, and radiation therapy clinicians to update the 2005 clinical practice guideline on the use of sentinel node biopsy (SNB) for patients with early-stage breast cancer.

Methods

The American Society of Clinical Oncology convened an Update Committee of experts in medical oncology, pathology, radiation oncology, surgical oncology, guideline implementation, and advocacy. A systematic review of the literature was conducted from February 2004 to January 2013 in Medline. Guideline recommendations were based on the review of the evidence by Update Committee.

Results

This guideline update reflects changes in practice since the 2005 guideline. Nine randomized clinical trials (RCTs) met systematic review criteria for clinical questions 1 and 2; 13 cohort studies informed clinical question 3.

Recommendations

Women without sentinel lymph node (SLN) metastases should not receive axillary lymph node dissection (ALND). Women with one to two metastatic SLNs planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases). Women with SLN metastases who will undergo mastectomy should be offered ALND. These three recommendations are based on RCTs. Women with operable breast cancer and multicentric tumors, with ductal carcinoma in situ (DCIS) who will undergo mastectomy, who previously underwent breast and/or axillary surgery, or who received preoperative/neoadjuvant systemic therapy may be offered SNB. Women who have large or locally advanced invasive breast cancer (tumor size T3/T4), inflammatory breast cancer, or DCIS (when breast-conserving surgery is planned) or are pregnant should not undergo SNB. These recommendations are based on cohort studies and/or informal consensus. In some cases, updated evidence was insufficient to update previous recommendations.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines on use of sentinel node biopsy (SNB) for patients with early-stage breast cancer in a guideline published in 2005. At the time of publication, there was only one published randomized clinical trial (RCT), by Veronesi et al.¹ There were no axillary recurrences in patients who had tumor-free nodes and did not undergo axillary lymph node dissection (ALND), and the short-term survival was similar for those with tumor-free nodes treated with ALND. However, the study was underpowered for overall

survival (OS). ASCO guidelines are updated at intervals determined by an Update Committee of the original Expert Panel. Since the publication of the original guideline, additional randomized trial results have become available. Practice has changed, but several issues remain unresolved, especially with regard to the accuracy of SNB in special circumstances. A formal update of the systematic review for this guideline and recommendations was conducted. This guideline summarizes the updated literature search; it also reviews and analyzes new data regarding the recommendations since the systematic review for the previous update. Since 2005, ASCO has updated some of its guideline

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Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline Update provides recommendations with review and analysis of the relevant literature for each recommendation. Additional information, which may include data supplements, slide sets, patient versions, clinical tools, and resources, is available at www.asco.org/guidelines/breastnsb.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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THE BOTTOM LINE

ASCO GUIDELINE UPDATE

Recommendations for Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: ASCO Clinical Practice Guideline Update**Guideline Question**

- How should the results of sentinel node biopsy (SNB) be used in clinical practice? What is the role of SNB in special circumstances in clinical practice? What are the potential benefits and harms associated with SNB?

Target Audience

- Medical oncologists, radiation oncologists, pathologists, surgeons, oncology nurses, patients/caregivers, and guideline implementers.

Methods

- A comprehensive systematic review of the literature was conducted, and an Update Committee was convened to review the evidence and develop guideline recommendations. The guide for rating recommendations and strength of evidence is provided in the Methodology Supplement.

Recommendations

- Recommendation 1: Clinicians should not recommend axillary lymph node dissection (ALND) for women with early-stage breast cancer who do not have nodal metastases. Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.
- Recommendation 2.1: Clinicians should not recommend ALND for women with early-stage breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery (BCS) with conventionally fractionated whole-breast radiotherapy. Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.
- Recommendation 2.2: Clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found on SNB who will receive mastectomy. Type: evidence based; benefits outweigh harms. Evidence quality: low. Strength of recommendation: weak.
- Recommendation 3: Clinicians may offer SNB for women who have operable breast cancer who have the following circumstances:
 - 3.1: Multicentric tumors. Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.
 - 3.2: Ductal carcinoma in situ (DCIS) when mastectomy is performed. Type: informal consensus; benefits outweigh harms. Evidence quality: insufficient. Strength of recommendation: weak.
 - 3.3: Prior breast and/or axillary surgery. Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: strong.
 - 3.4: Preoperative/neoadjuvant systemic therapy. Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.
- Recommendation 4: There are insufficient data to change the 2005 recommendation that clinicians should not perform SNB for women who have early-stage breast cancer and are in the following circumstances:
 - 4.1: Large or locally advanced invasive breast cancers (tumor size T3/T4). Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.
 - 4.2: Inflammatory breast cancer. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.
 - 4.3: DCIS when breast-conserving surgery is planned. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.
 - 4.4: Pregnancy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

Qualifying Statements

- Clinicians may perform SNB for DCIS diagnosed by minimally invasive breast biopsy: one, when mastectomy is planned, because this precludes subsequent SNB at a second operation; two, when physical examination or imaging shows a mass lesion highly suggestive of invasive cancer; or three, the area of DCIS by imaging is large (≥ 5 cm). SNB may be offered before or after neoadjuvant systemic therapy (NACT), but the procedure seems less accurate after NACT. This update deleted a recommendation for patients having undergone prior nononcologic breast surgery or axillary surgery because of insufficient data to inform a recommendation.

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THE BOTTOM LINE (CONTINUED)

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/guidelines/breastsnb. Patient information is available at www.cancer.net.

methodology, including the phrasing of recommendations, which is reflected in this document.² Data Supplement 7 provides both the 2005 and 2013 recommendations.

Positive lymph nodes can contain metastases or be tumor involved, and the latter terms are more accurate; therefore, this guideline uses the terms metastasis or metastatic. The term tumor free is more accurate than the term negative and is therefore used. In addition, ALND is defined as level I or II axillary dissection.

GUIDELINE QUESTIONS

Overarching Clinical Question

How should the results of SNB be used in clinical practice, and what are the potential benefits and harms associated with SNB?

Clinical Question 1

Can ALND be avoided in patients who have tumor-free (ie, negative) findings on SNB?

Clinical Question 2

Is ALND necessary for all patients with metastatic findings on SNB?

Clinical Question 2.1. For women with metastatic sentinel lymph nodes (SLNs) planning to undergo breast-conserving surgery (BCS) with whole-breast radiotherapy?

Clinical Question 2.2. For women with nodal metastases who are planning to undergo mastectomy?

Clinical Question 3

What is the role of SNB in special circumstances in clinical practice (Data Supplement 8)?

METHODS

The recommendations were developed by an Update Committee (Appendix Table A1, online only) with multidisciplinary representation using a systematic review of phase III RCTs, some observational studies, and clinical experience as a guide. Most of the Clinical Question 1 and 2 recommendations were evidence based and used publications found in a literature search from 2004 to January 2013.

The Update Committee only considered observational data for specific circumstances, and not all of the special circumstances were addressed in this guideline update. In some selected cases where evidence was lacking, but there was a high level of agreement among Update Committee members, informal consensus was used (as noted in the Bottom-Line Box).

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria:

- Population: women with early-stage breast cancer.
- For Clinical Questions 1 and 2, fully published or recent meeting presentations of English-language reports of phase III RCTs or rigorously conducted systematic reviews or meta-analyses. Trials with a population of women with early breast cancer that compared SNB with the standard treatment of ALND; this included studies comparing SNB alone with SNB plus ALND, for those patients with negative SLNs.
- For special circumstances, prospective comparative cohort trials were accepted (criteria listed in Data Supplement 8).

Articles were excluded from the systematic review if they were: (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; and (3) published in a language other than English. The guideline recommendations were crafted, in part, using Guidelines Into Decision Support (GLIDES) methodology.² Ratings for the type and strength of recommendation, evidence, and potential bias are provided in the Methodology Supplement (www.asco.org/guidelines/breastsnb).

Detailed information about the methods used to develop this guideline update, regarding the Update Committee composition, guideline development process, and steps taken in the systematic review and recommendation development process, is available in further detail in the Methodology and Data Supplements at www.asco.org/guidelines/snbbreast.

Guideline Disclaimer

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Guideline and Relationships With Companies

The Update Committee was assembled in accordance with the ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (ie, Procedures, summarized at <http://www.asco.org/rwc>). Members of the committee completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the committee did not disclose any such relationships.

RESULTS

As summarized in Table 1 and Data Supplement 1 (Tables 1A and 2A), a total of nine RCTs were deemed eligible for inclusion in the systematic review of the evidence for Clinical Questions 1 and 2; 13 cohort studies were deemed eligible for Clinical Question 3, as presented in Data Supplements 1 and 2 (Tables 1B, 2B, and 3). No phase II studies, meta-analyses, or other systematic reviews were found that met the ASCO systematic review criteria for this guideline (Data Supplement 8 addresses special circumstances). These studies comprise the evidentiary basis of the guideline recommendations. The identified trials were published between 2004 and 2013. The randomized trials compared similar interventions. The primary outcome for four of the trials for Clinical Question 1 was therapeutic efficacy,^{3,6,9,13} as it was in two of the trials for Clinical Question 2.^{4,12} Morbidities and quality of life (QOL) were the primary outcomes for the three other studies,^{5,7,8,11} although they were framed in a variety of ways, such as recurrence-free survival, event-free survival (EFS), all-cause mortality, and so on. The cohort studies for Clinical Question 3 reported a mix of efficacy and adverse effect–related outcomes (Data Supplement 2). Characteristics of the study participants are listed in Data Supplement 1 (Tables 2A and 2B).

Study Quality

As summarized in Table 2, study quality was formally assessed for the nine RCTs identified. Design aspects related to individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on, generally indicating a low to intermediate potential risk of bias for most of the identified evidence. Follow-up times varied among studies, lowering the comparability of the results. The Methodology Supplement provides for definitions of ratings for overall potential risk of bias.

Outcomes and Adverse Events

Data on key outcomes of interest and key adverse events are listed in Table 1 (RCTs) and in Data Supplement 2 (cohort studies).

OVERARCHING CLINICAL QUESTION

How should the results of SNB be used in clinical practice?

Nine RCTs were found to inform this recommendation. None of the trials showed any difference in mortality among participants who

underwent ALND or SNB for either those with lymph node metastases or tumor-free (negative) SLNs. One trial showed statistically significant longer disease-free survival (DFS)¹² with SNB, and one trial showed a statistically significant noninferiority outcome in deaths in those with metastatic nodes who did not undergo ALND.⁴ Clinical Question 2 is divided into two subquestions for women with SLN metastases compared with tumor-free nodes.

CLINICAL QUESTION 1

Can ALND be avoided in patients who have tumor-free (negative) SLNs?

RECOMMENDATION 1

Clinicians should not recommend ALND for women with early-stage breast cancer who do not have nodal metastases. Type: evidence based; benefits outweigh harms. Evidence quality: strong. Strength of recommendation: high.

Literature Review and Analysis

Seven RCTs have been published since the previous version of this guideline¹⁵ that prospectively investigated whether ALND can be avoided in patients who have tumor-free findings on SNB. These trials include: NSABP (National Surgical Adjuvant Breast and Bowel Project) B32,^{13,14,16,17} ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance),^{5,18,19} Sentinella/GIVOM (Gruppo Interdisciplinare Veneto di Oncologia Mammaria),^{6,20,21} Canavese et al,³ RACS (Royal Australasian College of Surgeons)/SNAC (Sentinel Node Versus Axillary Clearance),^{7,8,22,23} NCT00970983,^{9,10} and the Cambridge/East Anglia Study Group.¹¹ NSABP B32 produced four publications that met the systematic review selection criteria. These publications included results on OS, recurrence, adverse events, technical success, and performance. The ALMANAC study published four articles, which reported morbidities, QOL, recurrence, and performance. Three reports from Sentinella/GIVOM published results on morbidities, recurrence, OS/mortality, DFS, performance, adverse events, and QOL. Canavese et al published one article that reported recurrence, OS/mortality, EFS, morbidities, and false-negative rates (FNRs). The RACS/SNAC study was published in four reports on an interim analysis of the first 150 participants; results included morbidities, QOL, and FNRs. For NCT00970983, there were two articles, reporting recurrence, mortality/OS, DFS, and performance. The Cambridge/East Anglia Study Group published one article reporting on morbidities and QOL. (The IBCSG [International Breast Cancer Study Group] 23-01 is discussed under Clinical Question 2 because most of the patients had one to three micrometastases.)

Clinical Outcomes

This section summarizes the efficacy results from the trials published since the systematic review for the 2005 guideline for this clinical question. Five trials reported results on clinical/efficacy outcomes.^{3,5,6,9,13} In four of those five trials, survival outcomes were the primary end points.^{3,6,9,13} Of these four trials, NSABP B32 had the largest number of participants (N = 3,989). The second largest, Sentinella/GIVOM, had 697 participants, but the authors of this study felt it was too small to draw conclusions.

Table 1. RCTs: Outcomes

Study	Comparisons	No. of Patients Evaluated or Randomly Assigned*	Median Follow-Up	Recurrence	OS/Mortality	QOL and Adverse Events	FNR, NPV, and PPV	Overall Accuracy
Canavese et al ³ (2009)	SNB + ALND	110 of 124	5.5 years	5-year EFS (including recurrence), 94.5%; 95% CI, 90.9 to 98.1; <i>P</i> = .72 Annual rate of events: 16.2 per 1,000† 5-year EFS (including recurrence), 89.8%; 95% CI, 86.9 to 92.7; <i>P</i> = .72 Annual rate of events, 18.6 per 1,000† No axillary RR of SNB v SNB + ALND, 0.87; 95% CI, 0.38 to 2.01; <i>P</i> = .741	OS, 97.2%; 95% CI, 95.4% to 98.9% OS, 97.2%; 95% CI, 95.4% to 98.9%	NR	FNR (ALND), 6.84% NPV, 91.1% PPV, 71.1%	93%
Giuliano et al ⁴ (2011; ACOSOG Z0011)	SNB alone	436 of 446	6.3 years	5-year DFS, 83.9%; 95% CI, 80.2% to 87.9% 5-year LR, 1.6%; 95% CI, 0.7% to 3.3% 5-year LRR-free survival, 96.7%; 95% CI, 94.7% to 98.6%; <i>P</i> = .28 5-year DFS, 82.2%; 95% CI, 78.3% to 86.3% 5-year LR, 3.1%; 95% CI, 1.7% to 5.2%	5-year deaths, 42 of 426 5-year OS, 92.5%; 95% CI, 90.0% to 95.1%; <i>P</i> = .008 5-year deaths, 52 of 445 5-year OS, 91.5%; 95% CI, 89.1% to 94.5% HR, 0.79; 90% CI, 0.56 to 1.10† HR, 0.87; 90% CI, 0.62 to 1.23\$	QOL NR Higher for ALND than SLND-alone group (70% v 25%; <i>P</i> < .001) Lymphedema in ALND group significantly more common by subjective report (<i>P</i> < .001) and by objective assessment of arm circumference	NR	NR
Mansel et al ⁵ (2006; ALMANAC trial)	SNB only	495 of 478	12 months	Axillary, 1 Difference, 2.7%; 95% CI, -1.5% to 7.8%	At 12 months, seven deaths (two breast cancer specific) At 12 months, seven deaths (two breast cancer specific)	SNB group: overall patient-recorded OOL statistically significantly better (<i>P</i> = .003) † SNB group: overall patient-recorded OOL; TOI: 1 month after surgery, <i>P</i> < .001; 3, 6, and 12 months after surgery, <i>P</i> = .001 SNB group: FACT-B+4: change in score from baseline to 1 (<i>P</i> < .001), 3 (<i>P</i> = .001), 6 (<i>P</i> = .003), 12 (<i>P</i> = .002), and 18 months (<i>P</i> = .003) Arm functioning deterioration greater in ALND than in SNB group at each study time point (<i>P</i> < .001) Moderate or severe lymphedema reported more often by patients in ALND than in SNB group at 1, 3, 6, and 12 months after surgery (eg, 5% v 13% at 12 months; <i>P</i> < .001) RR, 0.37 (95% CI, 0.23 to 0.60) at 12 months for lymphedema for SNB compared with ALND group	FNR, 6.7%; 19 of 282 NPV, NR PPV, NR	97.6%; 782 of 803

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Table 1. RCTs: Outcomes (continued)

Study	Comparisons	No. of Patients Evaluated or Randomly Assigned*	Median Follow-up	Recurrence	OS/Mortality	QOL and Adverse Events	FNR, NPV, and PPV	Overall Accuracy
Zavagno et al ⁶ (2008; Sentinella/GIVOM)	SNB + ALND	345	56 months	5-year DFS, 87.6%; 95% CI, 83.3 to 90.9	5-year OS, 95.5%; 95% CI, 92.2 to 97.5	SNB group: mean change in arm volume at 12 months, 1.028; 95% CI, 1.016 to 1.039 ALND group: mean change in arm volume at 12 months, 1.028; 95% CI, 1.016 to 1.039 Lymphedema: SNB v ALND: RR, 0.37; 95% CI, 0.23 to 0.60; absolute rate, 5% v 13% Sensory loss: SNB v ALND: RR, 0.37; 95% CI, 0.27 to 0.50; absolute rate, 11% v 31%; <i>P</i> < .001 Higher rate of sensory deficit in ALND v SNB group (by self-assessment, at 12 months), 31% v 11%; percent of patients who had ≥ one arm problem 1 month post-surgery greater in SNB v ALND group RR, 0.37; 95% CI, 0.27 to 0.50; sensory deficit at 12 months in favor of SNB group ICBN nerve divided in 22.6% (88 of 390) of ALND v 5.3% (21 of 400) of SNB group (<i>P</i> < .001) SNB group: drain usage, length of hospital stay, and time to resumption of normal day-to-day activities after surgery were statistically significantly lower (<i>P</i> < .001) SNB group: axillary operative time reduced (<i>P</i> = .055)	FNR, 16.7% (18 of 108); 95% CI, 10.2 to 25.1 PPV, NR NPV, 92.3% (215 of 233); 95% CI, 88.1 to 95.4	94.4% (305 of 323); 95% CI, 91.3 to 96.7
Smith et al ⁷ (2009), Ung et al ⁸ (2004; RACS/SNAC)	ALND SNB + ALND (if SLN positive)	319 324	NR NR	5-year OS, 94.8%; 95% CI, 91.6 to 96.8 Death resulting from non-BC causes, 11 of 345 5-year DFS, 89.9%; 95% CI, 85.3 to 93.1; <i>P</i> = .769 Distant, 16 of 352 LRR, 3 of 352 Contralateral, 3 of 352	NR NR Death resulting from non-BC causes, 6 of 352	Shoulder pain (SNB/ALND): mean OR, 0.74; 95% CI, 0.5 to 1.1; <i>P</i> = .11 Restrictions of shoulder mobility (SNB/ALND): mean OR, 0.55; 95% CI, 0.3 to 0.9; <i>P</i> = .016 Numbness (SNB/ALND): mean OR, 0.51; 95% CI, 0.4 to 0.7; <i>P</i> < .001 Axillary clearance: mean, 4.4; SE, 0.4; SLN-based management: mean, 2.9; SE, 0.4; mean difference between groups: mean, 1.5; SE, 0.6; <i>MWW</i> , <i>P</i> < .001 Patient report: routine axillary clearance: mean, 4.4; SE, 0.4; SLN-based management: mean, 2.9; SE, 0.4; Mean difference between groups: mean, 1.5; SE, 0.6; <i>MWW</i> , <i>P</i> < .001	FNR, 5% (interim) NPV, 98% (interim) PPV, 95% (interim)	NR

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Table 1. RCTs: Outcomes (continued)

Study	Comparisons	No. of Patients Evaluated or Randomly Assigned*	Median Follow-Up	Recurrence	OS/Mortality	QOL and Adverse Events	FNR, NPV, and PPV	Overall Accuracy
Veronesi et al ^{9,10} (2010; NCT00970983)	SNB + ALND	257	102 months	10-year EFS, 88.8%; 95% CI, 84.6 to 92.6 5-year DFS, 89.9%; 95% CI, 85.3 to 93.1; <i>P</i> = .769 Distant, 20 of 257 LRR, 4 of 257 Supercavium, 2 of 257 Contralateral, 10 of 257	OS, 89.7%; 95% CI, 85.5 to 93.8; <i>P</i> = .15 Deaths (BC), 14 of 257 Deaths (non-BC), 9 of 257		FNR, 8%; 95% CI, 3 to 15	
	SNB + ALND (if SLN positive)	259		10-year EFS, 89.9%; 95% CI, 85.9 to 83.9 5-year DFS, 89.9%; 95% CI, 85.3 to 93.1; <i>P</i> = .769 Distant, 17 of 259 LRR, 4 of 259 Axillary, 2 of 259 Contralateral, 9 of 259	OS, 93.5%; 95% CI, 90.3 to 96.8; <i>P</i> = .15 Deaths (BC), 11 of 259 Deaths (non-BC), 4 of 259			
Purushotham et al ¹¹ (2005; Cambridge/East Anglia Study Group)	SNB alone (SLN negative) SNB + ALND (control) SNB + ALND (if SLN positive)	86 155, 144 of 155 underwent follow-up 143; 57 of 143 comprised control group; 139 of 143 underwent follow-up	12 months	NR	NR	SF-36: mean difference, 3.7; 95% CI, 1.2 to 6.1; <i>P</i> = .001 In SNB + ALND (if SLN positive) group: Physical functioning score, 3.2; 95% CI, 1.1 to 5.4; <i>P</i> = .003 (higher) Vitality score, 3.7; 95% CI, 1.1 to 6.2; <i>P</i> = .004 (higher) GSI scale: somatization lower (<i>P</i> = .001) MAC scale: NS Depression and anxiety: NS Lymphedema: mean OR, 0.30; 95% CI, 0.18 to 0.68; <i>P</i> = .004 Difference in arm volume change: mean, 35.4 mL; SE, 12.2; <i>P</i> = .004 Neurologic/sensory deficits: overall fewer sensory findings with SNB + ALND; <i>P</i> < .001 Shoulder impairment: reduction in mobility always lower on average in study group (less impairment); significant only for flexion (<i>P</i> = .04)	NR	NR

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Table 1. RCTs: Outcomes (continued)

Study	Comparisons	No. of Patients Evaluated or Randomly Assigned*	Median Follow-Up	Recurrence	OS/Mortality	QOL and Adverse Events	FNR, NPV, and PPV	Overall Accuracy
Galimberti et al ¹² (2013; IBCSG 23-01)	ALND only (after SNB)	464	5.0 years	DFS, 84.4%; 95% CI, 80.7 to 88.1; P = .0042	5-year OS, 97.5%; 95% CI, 96.0 to 99.2	QOL NR Lymphedema: ALND, 13% (59 of 464); no ALND, 15% (15 of 467); P < .001	NR	NR
	No ALND (after SNB)	467		LRR, 10 of 464 Regional, 1 of 464 Distant, 34 of 464 Axillary, 1 of 464 DFS, 87.8%; 95% CI, 84.4 to 91.2; P = .0042	All-cause mortality/deaths, 4% (19 of 464) 5-year OS, 97.5%; 95% CI, 95.8 to 99.1	Sensory neuropathy: ALND, 18% (82 of 463); no ALND, 12% (65 of 467); P = .012 Motor neuropathy: ALND, 8% (37 of 464); no ALND, 3% (13 of 467); P < .001 Infections: ALND, 1 of 464 Patients with reported long-term surgical events (grade 3-4) included one sensory neuropathy (grade 3), three lymphoedema (two grade 3 and one grade 4), and three motor neuropathy (grade 3), all in group undergoing ALND, and one grade 3 motor neuropathy in group without ALND; one serious adverse event was reported: postoperative infection in axilla in group with ALND	NR	NR
				LRR, 8 of 467 Regional, 5 of 467 Distant, 25 of 467 Axillary, 4 of 467 HR, 0.78; 95% CI, 0.55 to 1.11; P = .0042 (no ALND v ALND)	All-cause mortality/deaths, 4% (17 of 467) HR, 0.89; 90% CI, 0.52 to 1.54; P = .73			

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Table 1. RCTs: Outcomes (continued)

Study	Comparisons	No. of Patients Evaluated or Randomly Assigned*	Median Follow-up	Recurrence	OS/Mortality	QOL and Adverse Events	FNR, NPV, and PPV	Overall Accuracy
Krag et al ^{13,14} (2010; NSABP B32; interim report, n = 150)	SNB alone (if SLN negative)	2,011	95.6 months (mean)	Total events, 16.7%; 336 of 2,011 events DFS, 16.7%; 336 of 2,011	8-yr OS, 90.3%; 95% CI, 88.9 to 91.8 HR, 1.19; 95% CI, 0.95 to 1.49; P = .13†	QOL NR Allergic reaction, 8% (blue dye) Shoulder abduction deficits ≥ 10% peaked at 1 week for SNB + ALND (75%) and SNB (41%) groups Arm volume differences ≥ 10% at 36 months were evident for SNB + ALND (14%) and SNB (8%) groups Numbness and tingling peaked at 6 months for SNB + ALND (49% and 23%) and SNB (15% and 10%) groups	FNR, 38.6% (268 of 694); 95% CI, 35.0 to 42.4 NPV, 9.8% (75 of 766); 95% CI, 7.8 to 12.1 PPV, NR	97.1% (2,544 of 2,619); 95% CI, 96.4% to 97.7% (of 75 patients with negative SNB with node-positive ALND)
	SNB + ALND	1,975		Regional node, 0.7%; 14 of 2,011 Contralateral, 2.2%; 44 of 2,011 Total events, 16%; 315 of 1,975 DFS, 315 of 1,975 Distant, 2.8%; 55 of 1,975 LR, 2.7%; 54 of 1,975 Regional node, 0.4%; 8 of 1,975 Contralateral, 2.8%; 56 of 1,975	8-year OS, 91.8%; 95% CI, 90.4 to 93.3† HR, 1.20; 95% CI, 0.96 to 1.50; P = .12† EFS, 84.1%; 1,660 of 1,975 Deaths, 7%; 140 of 1,975 Deaths (no BC), 2.3%; 5 of 1,975			

Abbreviations: ACOSOG, American College of Surgeons; ALMANAC, Axillary Lymphatic Mapping Against Nodal Axillary Clearance; ALND, axillary lymph node dissection; BC, breast cancer; DFS, disease-free survival; EFS, event-free survival; FACT-B+4, Functional Assessment of Cancer Therapy-Breast, scale version 4; FNR, false-negative rate; GIVOM, Gruppo Interdisciplinare Veneto di Oncologia Mammaria; GSI, Global Severity Index; HR, hazard ratio; IBCSG, International Breast Cancer Study Group; LR, local recurrence; LRR, locoregional recurrence; MAC, Mental Adjustment to Cancer; NPV, negative predictive value; NR, not reported; NS, not significant; NSABP, National Surgical Adjuvant Breast and Bowel Project; OR, odds ratio; OS, overall survival; PGWB, Psychological General Well Being Index; PPV, positive predictive value; QOL, quality of life; RACS, Royal Australasian College of Surgeons; RCT, randomized controlled trial; RR, risk ratio; SF-36, Short Form 36; SLN, sentinel lymph node; SNAC, Sentinel Node Versus Axillary Clearance; SNB, sentinel node biopsy; TOI, Trial Outcomes Index.

*Evaluated and/or randomly assigned with follow-up.
†Includes deaths.
‡Unadjusted HR.
§Adjusted HR for adjuvant therapy (chemotherapy, endocrine therapy, and/or radiation therapy) and age.
||Beck Depression Inventory.
¶State-Trait Anxiety Inventory
#European Organisation for Research and Treatment of Cancer Breast Cancer Module (EORTC-QLM BR23).

Table 2. RCTs: Quality Assessment

Study	Adequate Randomization	Concealed Allocation	Sample Size	Comparable Groups	Blinded	Validated and Reliable Measures	Adequate Follow-Up	Insignificant COIs	Overall Risk of Bias
Canavese et al ⁵ (2009)	X	?	—	X	—	X	?	?	?
Giuliano et al ⁴ (2011; ACOSOG Z0011)	?	?	X	X	Partially	X	?	X	Low
Mansel et al ⁶ (2006; ALMANAC trial)	X	X	X	X	—	Partially	X	X	?
Zavagno et al ⁶ (2008; Sentinella/GIVOM)	X	Partially	X	X	—	Partially	?	X	Low
Smith et al ⁷ (2009)	?	—	X	X	—	X	?	X	Intermediate*
Smith et al ⁷ (2009), Ung et al ⁸ (2004; RACS/SNAC)	?	?	X	?	Partially	—†	?	X	?
Veronesi et al ^{9,10} (2010; NCT00970983)	X	X	X	X	—	X	?, partially	X	Low
Purushotham et al ¹¹ (2005; Cambridge/East Anglia Study Group)	X	X	X	X	Partially; was not double blind	X	X	X	Low
Galimberti et al ¹² (2013; IBCSG 23-01)	X	?	Partial	X	—	X	X	X	Intermediate
Krag et al ^{13,14} (2010; NSABP B32)‡	X	?	?	X	?	X	X	Not relevant	Low

NOTE. X indicates criterion was met; — indicates insufficient detail, not reported, and/or uncertain risk of bias.

Abbreviations: ACOSOG, American College of Surgeons; ALMANAC, Axillary Lymphatic Mapping Against Nodal Axillary Clearance; COI, conflict of interest; GIVOM, Gruppo Interdisciplinare Veneto di Oncologia Mammaria; IBCSG, International Breast Cancer Study Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; RACS, Royal Australasian College of Surgeons; RCT, randomized controlled trial; SNAC, Sentinel Node Versus Axillary Clearance.

*Several items were not reported; trial not fully published.

†Interim analysis.

‡Interim publication (n = 150).

Survival/mortality. Of the five trials reporting OS and/or mortality, none of the studies reported statistically significant differences.^{3,6,5,9,16} For example, the largest study¹³ reported an actuarial 8-year survival rate for SNB and ALND of 91.8% (95% CI, 90.4 to 93.3), compared with 90.3% (95% CI, 88.8 to 91.8) for SNB alone. All-cause mortality was 4% in each arm.¹⁶

DFS/EFS. Of the four trials reporting DFS and/or EFS, none reported statistically significant differences.^{3,6,9,16}

Recurrence. Five trials reported on recurrence.^{3,5,6,9,16} They found that the rates of in-breast local recurrence, axillary recurrence, and distant recurrence were similar with SNB alone and with SNB plus ALND. For example, Canavese et al³ showed the overall annual rate of events per 1,000 (including deaths) was 16.2 with SNB and 18.6 with ALND. In NSABP B32, with locoregional recurrence as the first event, local recurrence was 2% in both arms, and distant recurrence was similar.

Adverse events. Five trials reported adverse events.^{5-8,11,18,20} In most studies, results of adverse events/effects were higher for those with tumor-free SLNs who underwent ALND than for those who underwent only SNB. Important adverse effects included lymphedema, infections, seroma, and neurologic and sensory deficits, including paresthesia and shoulder pain and/or impairment of motion.

In the four studies reporting lymphedema, a clinically important adverse event, lymphedema was clearly identified to occur even with SNB alone but at lower rates than those found among patients undergoing ALND. In the ALMANAC trial, lymphedema was measured by participant self-assessment and reported as moderate or severe at 12 months in 1% with SNB versus 2% with ALND ($P < .001$).⁵ In another study, lymphedema was statistically significantly lower without ALND.⁶ The NSABP B32 study assessed lymphedema by measurement of arm volume \geq a 10% difference from baseline. Grade 3 and 4 rates of lymphedema were not notably different. Overall lymphedema was higher in ALND arm.²⁴

Another set of adverse events reported in several studies were neurologic/sensory deficits. In the four studies reporting these,^{5,6,11,13,20,21} the percentages of patients experiencing these deficits were statistically significantly lower in the SNB-alone arms.^{5,6,11,18,20} For example, residual arm tingling and numbness at 36 months were significantly lower in favor of SNB. Rates of sensory and motor neuropathy in NSABP B32 were higher with ALND. In some serious adverse-event categories, there were no significant differences. For example, in one study, seroma was stratified by nodal status, and the proportion of patients who developed a seroma with SNB was significantly smaller than the proportion in the SNB plus ALND control group; the difference in those requiring aspirations was also significant.¹¹ In NSABP B32, there was not a difference in the percentage of patients who had grade \geq 3 surgery-related events.

Other Outcomes

Performance. Six of the trials to date have reported on performance aspects of SNB.^{3,5-9,16} Performance outcomes extracted in the systematic review include FNR, negative predictive value (NPV), and overall accuracy. FNRs reported in the six studies ranged from approximately 4.6%⁹ (ASCO staff calculation) to 16.7%.⁶ Three studies reported NPVs ranging from 90.1%³ to 96.1%.^{6,16} Four studies reported overall accuracy of SNB results ranging from 93%³ to 97.6%.^{6,16,19}

QOL. Three studies reported on QOL.^{5,11,18,20} The trials used such instruments as the Trial Outcome Index (TOI), Functional Assessment of Cancer Therapy–Breast, scale version 4 (FACT-B+4), Psychological General Well Being Index (PGWB), Short Form–36 (SF-36), and the simple visual analog QOL, as well as tools for measuring psychological morbidity. Either there were no significant differences, or results favored the SNB-alone arm. For example, in the ALMANAC trial, there were statistically significantly better outcomes for participants in the SNB-alone arm; also reported were changes in FACT-B+4 scores favoring SNB alone.¹⁸

Clinical Interpretation

The Z0010 study²⁵ was not included in final systematic review, because it was a prospective multicenter cohort, not an RCT. Its primary end point was OS, and secondary end points included DFS and axillary recurrence; however, they were not reported in the Z0010 publication used in this guideline.²⁵ The study also measured adverse events at 30 days and at 6-month intervals up to year 3 and annually thereafter. A total of 5,539 patients were enrolled, and there were 5,327 available for analysis. In a multivariable analysis, age (at a cutoff of 70 years) was a predictor for axillary seroma. In another outcome of a multivariable analysis, decreasing age was associated with the presence of paresthesia.

CLINICAL QUESTION 2

Is ALND necessary for all patients with metastatic findings on SNB?

Literature Review and Analysis

This section summarizes the efficacy results from the trials published since the systematic review for the 2005 guideline for this clinical question. It is based on two RCTs that both reported efficacy and adverse-event results in patients with metastases in SLNs randomly assigned to either completion ALND or no ALND: ACOSOG (American College of Surgeons Oncology Group) Z0011⁴ and IBCSG 23-01.¹² The ACOSOG Z0011 investigators reported on recurrence, OS/mortality, DFS, and adverse events in four articles included in this systematic review. The IBCSG 23-01 investigators reported on recurrence, OS/mortality, DFS, and adverse events in one article published after the ASCO systematic review, but the Update Committee deemed it appropriate to include because of its confirmatory nature.

ACOSOG Z0011 was a noninferiority RCT in which 446 patients were randomly assigned to SNB with no further axillary treatment and 445 to SNB plus ALND. All patients had metastatic SLNs, and all had T1 or T2 tumors managed by lumpectomy and planned whole-breast irradiation. The extent of node involvement was micrometastatic (metastatic focus $<$ 2 mm) in approximately half of the study patients, but this information was not available for all trial participants. OS was the primary outcome. The primary outcome of IBCSG 23-01 was noninferiority in DFS, and this study was designed for patients with sentinel node micrometastases. It had a sample size of 964 participants; most participants had only one metastatic node. Consistent with the study design, 98% of the SLN tumors in both randomized arms had micrometastatic disease only. Results in IBCSG 23-01 were not analyzed by size of metastases. More than 80% of the participants in the ACOSOG Z0011 and IBCSG 23-01 trials had estrogen receptor-positive disease. Both of these studies were closed early because of failure to meet their accrual targets.

The recommendations in response to this clinical question were split into two separate recommendations. The first recommendation was crafted to reflect the eligibility criteria of Z0011 (women with early-stage breast cancer and one to two SLN metastases, who underwent BCS with whole-breast radiotherapy).

CLINICAL QUESTION 2.1

Is ALND necessary for all patients with metastatic findings on SNB planning to undergo BCS with whole-breast radiotherapy?

RECOMMENDATION 2.1

Clinicians should not recommend ALND for women with early-stage breast cancer and one or two SLN metastases who will undergo BCS with conventionally fractionated whole-breast radiotherapy. Type: evidence based; benefits outweigh harms. Evidence quality: strong. Strength of recommendation: high.

Literature Review and Analysis: Clinical Outcomes

Mortality. There was no apparent negative impact on mortality of omitting ALND (there was a statistically significant difference for noninferiority in mortality) after a median follow-up of 6.3 years. This was the first RCT to show these results. There were no such differences in IBCSG 23-01.

DFS. In Z0011, DFS was not statistically significant between arms. In IBCSG 23-01, there was a 3.4% reduction in DFS for SNB alone, which was statistically significant for noninferiority for ALND, with a 5-year follow-up. The per-protocol assessment of DFS was also statistically significant for noninferiority ($P = .0073$). However, this study randomly assigned only 934 of an accrual target of 1,960 participants.¹²

Recurrence. Both studies reported on recurrence. In locoregional, axillary, or distant recurrence, outcome results showed no significant differences.⁴ The differences were not statistically significant between arms in IBCSG 23-01 (eg, local recurrence rate at first event was 2% in both arms; distant recurrence was 7% for ALND and 5% for no ALND).¹²

Adverse events. There were statistically significant differences in rates of adverse events between study arms in both studies. Using slightly different numbers in the denominator than in the primary report extracted, another ACOSOG Z0011 publication reported on surgical complications. The protocol did not include objective measurements of arm volume. However, subjectively reported lymphedema was higher with ALND than in those with SNB alone. It was statistically significantly higher starting at 12 months, although not at 6 months or by arm measurement.²⁶ There was statistically significantly higher axillary seroma and paresthesia in the immediate ALND arm ($P < .001$), but not impaired range of movement (the latter two at 1 year), in a joint analysis of the cohort study Z0010 and RCT Z0011.²⁷ In a third-line report from Z0011, adverse surgical effects were 45% less in the SNB arm, including lymphedema ≥ 12 months.^{4,26,27} Infection in Z011 was reported as lower with SNB alone ($P = .0026$).²⁶

In IBCSG 23-01, there were lower overall rates of lymphedema (13% v 3%; $P \leq .001$) with no ALND. The percentages of patients experiencing neurologic/sensory deficits were also reported as higher with ALND (eg, motor neuropathy); however, the rates of grade 3 to 4

deficits were low in IBCSG 23-01.¹² It is important to note that adverse events were not stratified by micro- versus macrometastases in IBCSG 23-01. Infection was higher in the ALND arm ($P = .0016$) in Z0011; there was one case of infection in the ALND arm of IBCSG 23-01. There was not a subgroup of analyses of those whose SLN tumors were ≥ 2 mm in IBCSG 23-01 (2% in each arm).

Other Findings

Performance and QOL. There are not yet reports of findings on performance or QOL to inform this recommendation.

Clinical Interpretation

The eligibility criteria for Z0011 included a finding of a metastatic SLN by frozen section, touch preparation, or hematoxylin-eosin (HE) staining; all participants had lumpectomies. Exclusion criteria included having \geq three metastatic SLNs. Most patients entered the study after undergoing SNB, but 287 of 891 had not yet undergone SNB and were randomly assigned after surgeons found metastatic SLNs intraoperatively.⁴ The group with \geq three metastatic SLNs comprised 21% of the patients in the ALND arm and 3.7% in the SNB-alone arm; there was a higher proportion of patients with zero to two metastatic nodes in the SNB-alone arm. Although this was set as an eligibility criterion, some of the patients were enrolled before nodal status was known; if it turned out they had \geq three SLNs, these patients were included in the analysis.

By contrast, in IBCSG 23-01, $< 1\%$ of those in the ALND arm and no participant in the no-ALND arm had \geq three metastatic SLNs. According to the original eligibility criteria, participants could have only one micrometastatic SLN. The criteria for eligibility were broadened after the study began to include patients with \geq one metastatic SLN, with multicentric or multifocal tumors (formerly only unicentric), and whose largest lesion size was ≤ 5 cm (formerly ≤ 3 cm). Five percent of participants undergoing ALND and 4% of those randomly assigned to no ALND had two metastatic SLNs. Most of the participants had one metastatic node; however, 98% of the SLN tumors in both arms were ≤ 2 mm (micrometastatic).

In the expert opinion of the Update Committee, ALND can be avoided in cases of BCS, but only when conventionally fractionated whole-breast radiation therapy is planned. Although there were patients in the IBCSG study in the group managed without axillary dissection who underwent BCS with no radiation therapy (12 patients; 3%) or intraoperative partial-breast irradiation (80 patients; 19%), these subgroups were deemed too small to influence the decision by the Update Committee not to extend the recommendation beyond patients treated with conventionally fractionated whole-breast irradiation. This recommendation does not apply to patients whose axillary nodal positivity is documented by axillary fine-needle aspiration (FNA); clinicians may still perform SNB if the abnormal lymph node is removed. Data are insufficient to address whether FNA-positive patients can undergo SNB (under the assumption that resected SLNs represent the FNA-biopsied node) and then avoid ALND after resection of the metastatic SLN. Patients with FNA-positive nodes may have a higher axillary tumor burden compared with those with disease apparent on dissection of an SLN.

Clinicians may also consider this recommendation with caution in cases of women with large or bulky metastatic axillary SLNs and/or those with gross extranodal extension of the tumor. These were exclusion criteria for Z0011. The former were represented by few patient

cases in the ACOSOG Z0011 study, and the latter were specifically excluded. These uncommon patient cases may or may not carry a higher risk of axillary recurrence than those largely represented in the trial.

CLINICAL QUESTION 2.2

Is ALND necessary for all patients with metastatic findings on SNB who are planning to undergo mastectomy?

RECOMMENDATION 2.2

Clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found on SNB who will undergo mastectomy. Type: evidence based; benefits outweigh harms. Evidence quality: low. Strength of recommendation: weak.

Literature Review and Analysis

This recommendation is based on a subgroup of participants in IBCSG 23-01. Nine percent of the participants in each arm underwent mastectomy (ALND, $n = 44$; no ALND, $n = 42$). In the study analyses by subgroup, the results by type of surgery showed a lower risk of events with no ALND and BCS (\pm radiation therapy). Adverse events, QOL, and performance were not reported.

Clinical Interpretation

This recommendation is based on one subgroup of one study, involving a small number of participants. Adverse events were greater with ALND. There are currently conflicting data. There may be research in the future that could further inform this recommendation.

CLINICAL QUESTION 3

What is the role of SNB in special circumstances in clinical practice?

Note: Because of lack of evidence in many areas, the scope of this section was narrowed to the following circumstances. Recommendations from 2005 are available in Data Supplement 7. These recommendations are limited by the insufficiency and paucity of data.

RECOMMENDATION 3.1: MULTICENTRIC

Clinicians may offer SNB for women who have operable breast cancer and the following circumstance: multicentric tumors. Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.

Literature Review and Analysis

For the question of patients with multicentric tumors, the systematic review found five observational studies meeting the inclusion criteria. One study reported on survival and axillary recurrence; the results were not statistically significant. One reported on survival or DFS, two on recurrence, and three on performance. No significant differences were reported. One was a substudy of the ALMANAC trial (which was included as an RCT informing Clinical Question 1), in which all patients underwent SNB. There were no significant differences for either FNR or number of failed localizations for those with multifocal metastases.¹⁹ In another substudy of ALMANAC,²⁸ there were no significant differences in performance. There is one registry

study examining risk factors for axillary recurrence. The investigators divided patients with tumor-free SNB into four subgroups (small unifocal, large unifocal, small multifocal, and large multifocal [metastases]). There were axillary recurrences in 0.4% of the patients with small unifocal, 1.6% of those with small multifocal, and 0% of those with large unifocal or large multifocal tumors.²⁹

In another study, overall accuracy was similar between multicentric and unicentric groups; the FNR was lower for the multicentric group. NPV was 93.3% for multicentric and 97.9% for unicentric.³⁰

Clinical Interpretation

In the observational data reviewed, no meaningful differences were observed between studies using the terminology of multicentric or multifocal. The harms of omitting ALND do not seem to outweigh the benefits. Therefore, the Update Committee suggests that women with multicentric tumors be evaluated for SNB by the criteria in Recommendations 1 and 2.

RECOMMENDATION 3.2: DUCTAL CARCINOMA IN SITU

Clinicians may offer SNB for women who have operable breast cancer and the following circumstance: ductal carcinoma in situ (DCIS), when mastectomy is performed. Type: informal consensus; benefits outweigh harms. Evidence quality: insufficient. Strength of recommendation: weak.

Qualifying Statements

Clinicians may perform SNB for DCIS diagnosed by minimally invasive breast biopsy: one, when mastectomy is planned, because this precludes subsequent SNB at a second operation; two, when physical examination or imaging shows a mass lesion highly suggestive of invasive cancer; or three, when the area of DCIS by imaging is large (≥ 5 cm).

DCIS is characterized by proliferation of ductal epithelium without penetration or invasion through the ductal basement membrane. DCIS may be present as a component of an invasive cancer, or it may exist without any invasive cancer. In general, clinicians agree that pure DCIS without a coexisting invasive cancer cannot invade lymphatics and spread to regional nodes. However, because of the sampling error of minimally invasive biopsies, a substantial fraction of women identified with pure DCIS on a core-needle/vacuum-assisted minimally invasive biopsy prove to have some component of invasive cancer at surgical resection.³¹ However, there is currently no validated method to predict which patients will have invasive cancer in this setting. This has been used by some to justify performing SNB in all women with DCIS identified by core-needle/vacuum-assisted minimally invasive breast biopsy. Retrospective series show that a small percent have node metastases identified. However, a large majority of these are classified as micrometastases or clusters of isolated tumor cells (< 0.2 mm). Other data as reviewed in our update show that SNB can be performed in women with a prior surgical excision in the breast with success, and accuracy rates are equal to those in women with no prior breast excision.

Literature Review and Analysis

There were no studies that met criteria for evaluation of SNB for patients with DCIS, as confirmed by other recent systematic reviews.^{1,2} The rate of identification of metastatic SLNs defined in the

systematic reviews for patients proving to have pure DCIS on final resection is 0.9% for pN1 and 1.5% for pN1mic (micrometastases).

Clinical Interpretation

For women with a minimally invasive biopsy showing DCIS who are being treated with BCS, there is no evidence to support performing SNB (see Recommendation 4.3). Performing SNB places patients at risk for long-term complications including permanent lymphedema. SNB may be performed as a separate second procedure in the women in whom invasive cancer is found (reported in 10% to 20% of cases overall, approximately half of which are limited to microinvasive cancer). Exceptions may include cases where breast imaging or physical examination show an obvious mass characteristic of invasive cancer or a large area of calcification without a mass (eg, ≥ 5 cm) where the probability of finding invasive cancer on the resection specimen is high. In addition, when mastectomy is performed for DCIS, it may be warranted to perform SNB because of the possibility of finding an invasive cancer in the resected breast, and the disruption of the lymphatics by the mastectomy may preclude a subsequent SNB. These recommendations are primarily based on retrospective data. Therefore, the Update Committee does not endorse routine SNB for patients with DCIS undergoing BCS.

RECOMMENDATION 3.3: PRIOR SURGERY

Clinicians may offer SNB for women who have operable breast cancer and the following circumstance: prior breast and/or axillary surgery. Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: strong.

Literature Review and Analysis

The systematic review found two observational studies meeting the inclusion criteria. These studies did not report survival or DFS. One study reported recurrence and found a slightly higher recurrence rate for patients who had undergone prior biopsy. Both studies reported performance and did not find differences in those outcomes.

The first was a nonrandomized study that had two temporal phases, each including two groups (those with nonpalpable lesions and those with prior diagnostic biopsy). Distant recurrence for those with metastatic SLNs was as follows: prior biopsy, 5%; nonpalpable lesion, 1%. For patients with tumor-free SLNs, distant recurrence was as follows: prior biopsy, 2.0%; nonpalpable lesion, 0.5%. Axillary recurrence for those who had undergone prior surgery was zero in both those with metastatic SLNs and those with tumor-free SLNs. The SLN detection rate for those having undergone prior surgery was 96% versus 95%, and the FNR was 10% versus 5.6%.³² The second study was a nonrandomized study that included two groups: one group had undergone prior excisional biopsies, and the comparison group had undergone diagnostic core biopsies. Overall accuracy and sensitivity was 100% in the first group, and there were no false negatives.³³

Clinical Interpretation

Although there are no randomized data or other additional evidence that meet the eligibility criteria for this guideline update, the retrospective data are consistent with the feasibility and acceptable accuracy of performing SLN biopsy in patients who have undergone prior nononcologic breast/axillary surgery.

RECOMMENDATION 3.4: PREOPERATIVE/NEOADJUVANT SYSTEMIC THERAPY

Clinicians may offer SNB for women who have operable breast cancer and the following circumstance: preoperative/neoadjuvant systemic therapy (NACT). Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate.

Qualifying Statements

SNB may be offered before or after NACT, but the procedure seems less accurate after NACT.

Literature Review and Analysis

There were three cohort studies in the ASCO systematic review on preoperative systemic therapy and/or NACT. None reported survival/mortality, and one reported recurrence; the other data were on performance. Most of the studies did not show statistically significant differences in the reported outcomes between those who received NACT and those who did not,^{34,35} including FNR in the two studies that reported it.³⁴⁻³⁶

The analysis of the first study excluded patients who had SNB only (although included them in the study). Overall accuracy for those who had received preoperative chemotherapy was 95.9% versus 92.6% for those who had not received preoperative chemotherapy. Among patients whose SLNs were successfully identified, the overall accuracy rate was 93.7%. The FNR was not significantly different. For those who received preoperative chemotherapy, the NPV was 86.8%.³⁴

There was a second smaller study of patients with locally advanced breast cancer. The comparison group (patients with early-stage breast cancer) was from a previous RCT. The FNR for SNB after NACT was 5.2%. The third study was small and retrospective/prospective. The sole recurrence information it reported was distant recurrence in one of 52 patients who had received neoadjuvant chemotherapy. The median detection rate was nonsignificant between those who had not received neoadjuvant chemotherapy and those who had received it. The only statistically significant result was the number of lymph nodes removed, which was statistically significantly greater in the non-NACT group.³⁷

Clinical Interpretation

SNB may be offered before or after NACT, but the FNR is higher afterward, and therefore, the procedure seems less accurate after NACT. The outcome for patients who have metastatic nodes that then become negative has never been investigated. There were some other studies that were not included in the systematic review and, therefore, do not support the recommendation but are selectively discussed here.

One study did not fit the ASCO systematic review criteria, because it did not compare participants with and without NACT. As part of the NSABP B27 trial of NACT in participants with clinical stage II or III breast cancer, axillary dissection was required for all patients. The dates of this study coincided with ongoing studies from NSABP and ACOSOG of SNB in patients with clinical node tumor-free breast cancer. The technique was not standardized, and it was not included in the actual B27 study. Although SNB was not a component of the B27 study, the NSABP determined that 428 participants had SNB before the required ALND at the treating center. The NSABP elected to report the collective findings. However, the findings are limited by the

fact that the technique of SNB was selected by the treating surgeon and was not consistent (radioactive colloid alone, 15%; lymphazurin alone, 30%; both, 55%). At least one SLN was identified in 85% of patient cases. Among 343 patients with both SNB and ALND, 125 had metastatic nodes. Among those with tumor-free SLNs, 15 had metastatic nonsentinel nodes (FNR, 10.7%).³⁸

The benefits outweigh the harms in a given patient, because the patient has already received systemic therapy, and the impact of a false negative is unlikely to lead to omission of radiation therapy. Cells remaining in the SLNs after chemotherapy may be chemoresistant, and postoperative chemotherapy is variable and often not pursued. Radiation to the axilla may reduce the risk but is variably applied. For patients with metastatic nodes before NACT, the FNR with SNB after treatment may range from 10% to 30%, which, in the view of the Update Committee, is unacceptable. This may result in understaging and undertreatment of such patients. The SLN removed may not be the same node previously biopsied and found to be metastatic. The SENTINA (Sentinel Neoadjuvant) trial observed an FNR of 14.2% (and much higher rates if only one or two SLNs were removed).³⁹ More than half of patients who became clinically tumor free after NACT still had metastatic nodes pathologically. For example, the ACOSOG Z1071 trial found FNRs > 12% when only \geq two SLNs were removed.⁴⁰ There were FNRs of 31% if only one SLN was removed and 20% for single-agent lymphatic mapping (isotope or dye alone). Because of the publication dates of the reports, these studies were not included in the systematic review.

For patients who have received NACT and are considering undergoing SNB (\pm ALND), the most important measure of outcome is axillary local recurrence. The Update Committee urges caution about SNB after NACT because of the fact that no studies to date have reported a positive result in axillary local recurrence.

In the expert opinion of the Update Committee, SNB is not recommended in patients with T4d/inflammatory breast cancer who have received NACT (regardless of patients' clinical response to NACT), and data are insufficient to recommend SNB in patients with T4abc breast cancer whose cancer has been clinically downstaged after receiving NACT.

In addition, SLN biopsy after NACT is associated with a learning curve and surgical expertise.⁴¹ Lastly, decisions regarding the use of locoregional radiation therapy after NACT may be influenced by the histopathologic pre- as well as post-NACT nodal status. In the expert opinion of the Update Committee, data are presently insufficient, but the committee will take under consideration any data forthcoming regarding SNB in patients who have node metastases at presentation by pretreatment axillary FNA biopsy and are planning to receive NACT.

OTHER SPECIAL CIRCUMSTANCES

RECOMMENDATION 4.1: LARGE AND LOCALLY ADVANCED INVASIVE TUMORS (T3/T4)

There are insufficient data to change the 2005 recommendation that clinicians should not perform SNB for women who have early-stage breast cancer and have the following circumstance: large or locally advanced invasive breast cancer (tumor size T3/T4). Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

Literature Review and Analysis

There was one study found. The single small study meeting the inclusion criteria included 64 patients with locally advanced breast cancer. The comparison group (patients with early-stage breast cancer) was from a previous RCT. The overall accuracy results were 96.7% for patients with locally advanced breast cancer and 93.0% for those with early-stage breast cancer. Other results included FNRs (locally advanced, 5.1%; early stage, 5.8%), NPV (locally advanced, 91.3%; early stage, 91.1%), and sensitivity (locally advanced, 88.1%; early stage, 77.1%). It should be noted that because the control group was retrospective, it was on the borderline of the inclusion criteria. This study was also relevant to the preoperative/neoadjuvant systemic therapy question (Recommendation 3.4).³⁶

Clinical Interpretation

There were no new data found to support offering SNB to women with T3/T4d/inflammatory breast cancer that would change the 2005 recommendation. There are also no data to support SNB for patients with T4a/T4b/T4c breast cancer who will undergo primary surgery, because their clinical teams will likely administer primary systemic therapy/NACT, and the decision regarding SLN biopsy would be subject to the interpretation of data on primary systemic therapy/NACT.

RECOMMENDATION 4.2

There are insufficient data to change the 2005 recommendation that clinicians should not perform SNB for women who have early-stage breast cancer and have the following circumstance: inflammatory breast cancer. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

RECOMMENDATION 4.3

There are insufficient data to change the 2005 recommendation that clinicians should not perform SNB for women who have early-stage breast cancer and the following circumstance: DCIS, when BCS is planned. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.

RECOMMENDATION 4.4

There are insufficient data to change the 2005 recommendation that clinicians should not perform SNB for women who have early-stage breast cancer and have the following circumstance: pregnancy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

There were insufficient data to change some of the 2005 recommendations regarding performing SNB in several of the special circumstances, including women with early-stage breast cancer who have smaller tumors (T1/T2) and the presence of suspicious palpable axillary lymph nodes. Neither circumstance was included in the current systematic review. This update deleted a recommendation for patients who had undergone prior nononcologic breast surgery or axillary surgery because of insufficient data to inform recommendations.

Age should not be a factor when clinicians and patients are deciding whether to pursue SNB (\pm ALND). There are insufficient data to show there are any differences in outcome by chronologic age. There are no studies that meet the criteria for inclusion in this guideline addressing the questions of the accuracy, safety, and value of SNB

on older women. Many studies of SNB cited in this guideline included some older women. There is no reason to expect that SNB is not equally accurate in older women than in the general population of women included in these studies. As in all women with breast cancer, the need for axillary surgical staging with SNB or axillary dissection should be defined by: one, the requirement for lymph node staging to determine subsequent adjuvant therapies; two, the short- and long-term risks of the surgery; and three, the patient's objectives and intent for therapy.

Body mass index/body-surface area should similarly not be factors when clinicians and patients are deciding whether to pursue SNB (\pm ALND). Because there were insufficient data to indicate these were important clinical factors, they were not included in the final recommendations for this update.

Currently, there is controversy regarding the optimal management with radiation therapy of patients with metastatic SLNs on SNB. Almost all of the currently available data on omitting axillary dissection in patients with metastatic SLNs come from patients managed with BCS followed by conventionally fractionated whole-breast radiation therapy delivered in the supine position who have not received neoadjuvant systemic therapy. If more published evidence becomes available regarding the role of radiation therapy, the Update Committee or a subset of the committee may consider including it in any future updates of this guideline.

SPECIAL COMMENTARY

Occult Metastases, Isolated Tumor Cells, and Micrometastases

NSABP B32 included a double-blind cohort study of occult metastases for all patients with tumor-free SLNs enrolled onto the RCT.¹⁴ Occult metastases were isolated tumor cells (ITCs) or micrometastases, and rarely macrometastases, that were not detected on initial pathology and not used for clinical management but were detected with further evaluation. Detection of occult metastases is a method to test the clinical value of deeper levels and immunohistochemistry (IHC). Occult metastases are usually found only in deeper-cut HE sections, IHC stains, or molecular testing of an SLN thought to be tumor free based on the initial-level HE section.

The study detected occult metastases in 15.9% of 3,887 patients. Observed differences in patients with or without occult metastases for OS (1.2%; $P = .03$), DFS (2.8%; $P = .02$), and distant disease-free interval (2.8%; $P = .04$) were small, and although statistically significant, they were not clinically significant. The corresponding adjusted hazard ratios for death, any outcome event, and distant disease were 1.40 (95% CI, 1.05 to 1.86), 1.31 (95% CI, 1.07 to 1.60), and 1.30 (95% CI, 1.02 to 1.66), respectively. Five-year Kaplan-Meier estimates of OS among patients in whom occult metastases were detected and those without detectable metastases were 94.6% and 95.8%, respectively. Identification of occult metastases did not predict locoregional recurrence, DFS, or OS.

ACOSOG Z0010, a double-blind registration cohort study, also evaluated occult metastases. One additional level and IHC were performed, compared with two widely spaced levels and IHC on NSABP B32. Occult metastases were detected in 10.5% of 3,326 SLN specimens.²⁵ This trial permitted the institutional pathologists to get one or two deeper-cut HE levels in addition to the first cut off the top of the

paraffin block. Cytokeratin IHC was not allowed for clinical diagnosis. These differences may explain why the occult metastasis detection rate in the central laboratory was lower in the Z0010 trial compared with the B32 trial. No significant difference was detected for 5-year OS ($P = .64$) or DFS ($P = .82$) between patients with and without IHC-detected occult metastases. Neither B32 nor Z0010 support routine use of levels or IHC for detection of ITCs or micrometastases that may be present in SLN paraffin blocks that are tumor free on initial pathology evaluation of a single routinely stained section of the SLN. IBCSG 23-01 provides further evidence for this conclusion.¹² All SLNs were evaluated with multiple levels entirely through the SLN, and patients with \geq one SLN with micrometastasis (≤ 2.0 mm) were randomly assigned to axillary dissection or no further axillary surgery. There was no statistical difference in 5-year DFS between the groups.

Pathology

The update of this systematic review did not include pathology and/or pathology evaluation. Therefore, the following is based on the expert opinion of the Update Committee. Different studies have used different methods to evaluate SLNs and, thus, different criteria to define those with metastatic versus tumor-free nodes. Pathologists may have determined a tumor-free node with IHC^{5-9,11} or may have determined a tumor-free node without routine IHC.^{12,16} When IHC was used, this resulted in a higher percentage of nodes rated as positive (or metastatic) and of the inclusion of patients in the node-positive group with two to three micrometastases or ITC clusters as determined by either HE or IHC. This may have diluted apparent outcome differences between ALND and no ALND in some studies. The differences in method and definition among studies were largely regional (eg, US-based studies did not use IHC; European- and Australian-based studies used IHC).

As recommended in this guideline, SNB is the recommended surgical procedure for evaluation of clinically tumor-free regional nodes in patients with breast cancer, barring other exclusions. Clinicians, pathologists, and patients should be aware of the significance of identifying metastases in lymph nodes, even single cancer cells, as well as the reality that small metastases will be missed. Presence or absence of nodal metastases is the basis on which treatment decisions are made. In the expert opinion of the authors, pathologists, as part of their standard analysis, should quantify nodal tumor burden. Further discussion of the pathologic evaluation of SLNs from patients with breast cancer is available in Appendix 2 (online only).

PATIENT AND CLINICIAN COMMUNICATION

For SNB, as in all decision-making processes, appropriate communication is a critical component for the physician-patient relationship and for optimal patient compliance and outcome. Consideration of the patient's perspective, setting realistic expectations by discussing potential benefits and harms associated with SNB, explaining potential outcomes, and taking the time to understand what QOL means to the individual patient are key components of this communication.

With this as the guiding standard of practice, the Update Committee continues to recommend 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 and include

evidence-based information. 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 current status 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.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Minority racial/ethnic patients with cancer disproportionately experience comorbidities; they experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.⁴²⁻⁴⁵ Many other patients lack access to care because of their geography and distance from appropriate treatment facilities.

A literature search, although not systematic, was conducted to find literature addressing health disparities and SNB for patients with early-stage breast cancer. Six relevant studies were found. Some observational studies, including studies of SEER data, have indicated that women of color, including African American, Asians, and Hispanics, are less likely to undergo SNB than white women.⁴²⁻⁴⁶ For example, in an analysis of SEER data from 2000 to 2005 by Shah et al,⁴⁷ women with DCIS treated with mastectomy who were of Asian or Hispanic race/ethnicity were less likely to have undergone SNB. In a SEER/Medicare study of women undergoing BCS, African American and/or elderly women and those with lower socioeconomic were less likely to undergo SNB, and those associated with a National Cancer Institute cooperative group were more likely to undergo SNB.⁴⁸ In a third study, not undergoing SNB was associated with urbanity, as well as other racial/ethnic and socioeconomic factors. A fourth study found that the patients in the National Cancer Database from 2003 to 2005 age \geq 73 years were three times as likely not to undergo SNB or ALND, as well as showing disparities by racial/ethnic and insurance status.⁴⁹ A fifth study found a 33% difference in use of SNB between white and African American women ($P = .026$).⁴⁶ These findings occur in the context of health disparities that are well characterized in women with breast cancer.⁵⁰ Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have \geq two such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to ac-

count for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials, where study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCCs, any management plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making around guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan (common chronic conditions for patients with breast cancer are listed in Data Supplement 6).

Taking these considerations into account, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

EXTERNAL REVIEW

The pathology appendix was submitted to two external reviewers with content expertise, and it was agreed it would be useful in practice. Review comments were reviewed by D.L.W. and R.R.T. and integrated into the final manuscript.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed to be implemented in a variety of health settings. Barriers to implementation and application of the guideline recommendations include the need to increase awareness among front-line practitioners and cancer survivors and also the need to provide adequate services in the face of limited resources. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network and other ASCO communications. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology (JCO)* and *Journal of Oncology Practice*.

Given the multidisciplinary care discussed in this guideline and the importance of sharing the update with the many relevant stakeholders, it is suggested that community oncologists, surgical oncologists, and radiation oncologists as well as patient navigators and academic, community, and hospital-based cancer centers consider these guidelines. In addition, given that the majority of US cancer programs have cancer tumor boards or continuing medical education activities that include the many clinicians treating breast cancer, we encourage those programs to distribute and stimulate discussion of this guideline update. In expanding outreach of ASCO guidelines through the national tumor board system, we hope to speed the

sharing of this update as well as to stimulate coordinated multidisciplinary care decisions among medical oncologists, radiation oncologists, and surgical oncologists as well as patients, their advocates, and cancer program leaders. The American College of Surgeons, which accredits most US cancer programs, has included review of National Comprehensive Cancer Network guidelines for the diagnosis and treatment of cancer as quality measures in the past few years. Discussion of including ASCO guidelines and updates as part of this process would further increase the review and discussion of ASCO guidelines and likely speed the uptake of newly evaluated studies and guideline updates that can improve the quality of cancer care for patients.

LIMITATIONS OF RESEARCH AND FUTURE DIRECTIONS

Data were insufficient to make recommendations or to rate all recommendations as high on several of the categories of patients in special circumstances. These include patients with DCIS, T1/T2 tumors, T3/T4 tumors, inflammatory breast cancer, and T4d/inflammatory breast cancer who have received NACT; pregnant patients; SLN biopsy in patients with T4abc breast cancer whose cancer has been clinically downstaged after receiving NACT; SLN biopsy in patients who have node metastases at presentation by pretreatment axillary FNA biopsy and are planning to receive NACT; and patients with suspicious palpable axillary lymph nodes. Ongoing RCTs on NACT include NSABP B51 (ClinicalTrials.gov identifier: NCT01872975) and Alliance 11202.

Data are insufficient to address whether patients with FNA-positive results can undergo SNB (under the assumption that resected

SLNs represent FNA-biopsied nodes) and then avoid ALND after resection of the metastatic SLNs. In addition, additional data on SNB and mastectomy, the role of age, and communicating the choices to patients are needed, in addition to data on the role of radiation therapy. More research is needed and encouraged on the potential role and limitations of SNB in these settings.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

This guideline was published in *JCO*. Additional information, including an Appendix on Pathology, a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools, and resources, is available at www.asco.org/guidelines/breastnsb. Patient information is available there and at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Appendix

Appendix 2: Pathologic Evaluation of Sentinel Lymph Nodes From Patients With Breast Cancer

Donald L. Weaver and Roderick R. Turner for the American Society of Clinical Oncology Breast Cancer Sentinel Node Guideline Update Committee. Sentinel node biopsy (SNB) is the standard surgical procedure for evaluation of clinically tumor-free regional nodes in patients with breast cancer. Clinicians, pathologists, and patients should be aware of the significance of identifying metastases in lymph nodes, even single cancer cells, as well as the reality that small metastases will not always be detected. The presence or absence of nodal metastases is the basis on which treatment decisions are made. Pathologists, as part of their standard analysis, should quantify nodal tumor burden. Consistent categorical reporting, using the American Joint Commission on Cancer (AJCC)/Union on International Cancer Control (UICC) staging system, facilitates uniform communication with clinicians and analysis of outcomes.

Management of Gross Specimen

Pathologists receive either single lymph nodes dissected free of fat or axillary adipose tissue containing \geq one lymph node. The statements provided here are the expert opinions of the authors. Fatty nodules should be carefully dissected to identify all lymph nodes. The operating surgeon should supply the relative radioactive uptake or objective gamma counts to the pathologist and record them. Lymph nodes are inspected for blue color, measured, and cut into sections no thicker than 2.0 mm. Each sentinel lymph node (SLN) is submitted in a separate cassette or identified by colored ink to permit accurate assessment of total number of lymph nodes and number of involved lymph nodes; all nodal sections are submitted for microscopic examination. Diverting tissue from microscopic examination will decrease identification of metastases (Smith PA et al: *Mod Pathol* 12:781-785, 1999). Health risks for laboratory technicians and pathologists handling isotope-labeled SLN tissue are negligible because of the short half-life and limited penetration of technetium (Fitzgibbons PL et al: *Am J Surg Pathol* 24:1549-1551, 2000).

Intraoperative Assessment of SLNs

Intraoperative assessment of SLNs was used in the development of the modern sentinel node technique (Morton DL et al: *Arch Surg* 127:392-399, 1992). It allows immediate axillary dissection in patient cases with a tumor-positive SLN. An understanding of the strengths and limitations of intraoperative examination of SLNs is critical (Van Diest PJ et al: *Histopathology* 35:14-18, 1999). Approximately 75% to 85% of patients considered for SNB have tumor-free lymph nodes in permanent sections. In the 15% to 25% with metastatic nodes, one third to one half will be missed intraoperatively (false negative) because of sampling limitations and the challenge of detecting micrometastases. Many institutions omit intraoperative assessment for economic reasons and concerns about test sensitivity. Each institution should establish a policy on intraoperative assessment or deferral to permanent sections. Both approaches are legitimate providing patients are informed of the possibility and risks of immediate or second surgery to complete axillary dissection. Completion of axillary dissection is not necessary for isolated tumor cell clusters (ITCs), and many women may elect no further surgery when only micrometastases are identified.

Intraoperative assessment may be by gross inspection, imprint cytology, evaluation of cells scraped from the nodal cut surface, or frozen section. Grossly metastatic SLNs are the nodes most likely to be associated with metastatic nonsentinel nodes. Immediate cytology or frozen section can confirm suspicious gross appearances. SLN cut surfaces 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. Pathologists should report suspicious results as tumor free or no definite tumor and defer to paraffin sections.

Intraoperative frozen sections can carry the risk of significant destruction of potentially diagnostic tissue. Frozen section evaluation can provide data on size of metastases not possible by cytologic evaluation. The quality of frozen tissue preparations may not be as high 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

A single hematoxylin-eosin (HE) –stained full-face section from each submitted SLN paraffin block can identify macrometastases and a high proportion of micrometastases (Weaver DL: *Mod Pathol* 23:S26-S32, 2010; Weaver DL et al: *Am J Surg Pathol* 33:1583-1589, 2009). Outcomes from large clinical trial cohorts have not shown any benefit from identifying micrometastases or ITCs (Giuliano AE et al: *JAMA* 306:385-393, 2011).^{7,16} Widely spaced step sections from the block (top level plus one or two sections cut at 500-micron intervals into the block) enhance detection of micrometastases and may compensate for SLNs cut thicker than 2.0 mm (Weaver DL et al: *Am J Surg Pathol* 33:1583-1589, 2009). Superficial serial sections limit sampling to the upper levels of the block. If the SLN has been grossly sectioned as recommended, a single section will detect virtually all macrometastases ($>$ 2.0 mm) and most cases of micrometastases ($>$ 0.2 to 2.0

mm; Turner RR: *Semin Breast Dis* 5:35-40, 2002; Viale G et al: *Cancer* 85:2433-2438, 1999; Weaver DL et al: *Cancer* 88:1099-1107, 2000). This sectioning technique will also detect ITCs and clusters (≤ 0.2 mm) in some patients, particularly if immunohistochemical analysis is used.

Immunohistochemistry

Immunohistochemistry may facilitate scanning of nodal sections and also enhances identification of micrometastases and ITCs. However, detection of micrometastases and ITCs does not predict recurrence or improve survival (Giuliano AE et al: *JAMA* 306:385-393, 2011).^{7,16} Thus, although micrometastases and ITCs have differing prognostic significance, strategies to enhance their detection are not necessary or required. Immunohistochemistry using anticytokeratin antibodies may be useful for confirming or excluding suspicious findings on HE stains.

Pathology Reporting of SLNs

Pathologists should provide sufficient information in their pathology reports to facilitate accurate cancer staging using the criteria of the current AJCC/UICC system (Edge SB et al: *AJCC Cancer Staging Manual* [ed 7]. New York, NY, Springer, 2010). This includes documentation of nodal tumor burden. If any nodal metastasis is larger than 2.0 mm, total number of metastatic nodes determines N category. Special rules apply if internal mammary, supraclavicular, or infraclavicular nodes contain tumor. Micrometastases have an upper and lower size limit and are individual tumor deposits larger than 0.2 mm but no larger than 2.0 mm. The lower size limit accommodates the frequency of small tumor deposit identification in SLN. When the largest confluent focus of nodal tumor is no larger than 0.2 mm, deposits are classified as ITC clusters. When more than 200 single cells are identified in a single cross-section of a SLN, a pathologist may classify the node as a micrometastasis. Micrometastases are coded as pN1mi. ITCs or cell clusters are coded as pN0 (i+). Examples of this format follow:

Example 1 (level one and two axillary dissection):

“One of 12 lymph nodes positive for metastatic tumor (1/12; AJCC: pN1a); largest metastasis measures 4.5 mm.”

Example 2 (sentinel node biopsy):

“One of three lymph nodes positive for micrometastatic tumor (1/3; AJCC: pN1mi [sn]); largest metastasis measures 1.5 mm.”

Example 3 (sentinel node biopsy):

“Two of three lymph nodes positive for isolated tumor cell clusters (2/3; AJCC: pN0 [i+; sn]); largest metastasis measures 0.1 mm.”

The (i+) notation indicates that a node contains ITC clusters, whereas pN0 indicates prognosis is similar to that of patients with tumor-free nodes. Careful attention should be given to accurately reporting the correct number of metastatic nodes. Bisected, trisected, or serially sectioned metastatic SLNs may be over-recorded absent 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.

Summary

- All SLNs and incidental nonsentinel nodes require special attention.
- Count and measure submitted nodes, and note and record blue coloration and the relative radioactive uptake reported by the surgeon.
- Intraoperative evaluation of SLNs may involve inspection of cut faces of the node, cytology of node imprints, or cell smears or frozen sections. Evaluation of SLNs is likely more accurate on the basis of paraffin sections.
- Nodes should be cut no thicker than 2 mm. A full-face cross-section of each SLN slice should be prepared and examined with HE.
- Cytokeratin staining is not regarded as a routine requirement for the evaluation of SLN from breast cancer patients.
- Reports should indicate the size of the largest tumor deposit in each SLN (isolated tumor cell clusters, micrometastases, macrometastases, and so on) and the presence or absence of extranodal soft tissue or vascular invasion using current AJCC/UICC criteria.

It should be noted that the molecular testing section has been deleted because this is not often used in the clinical setting, but rather in the research setting, which is outside the scope of this Appendix and Clinical Practice Guideline Update.

Table A1. Update Committee Membership

Member	Affiliation	Role/Area of Expertise
Gary H. Lyman, MD, MPH, FASCO, co-chair	Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA	Medical oncology
Armando E. Giuliano, MD, co-chair	John Wayne Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA	Surgical oncology
Al B. Benson III, MD	Northwestern University, Chicago, IL	Medical oncology
Linda Bosserman, MD, FACP	Wilshire Oncology Medical Group, Rancho Cucamonga, CA	Guideline implementation (PGIN)
Harold J. Burstein, MD, PhD	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Hiram S. Cody III, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Surgical oncology
Stephen B. Edge, MD	Baptist Cancer Center, Memphis, TN	Surgical oncology
James A. Hayman, MD	University of Michigan, Ann Arbor, MI	Radiation oncology
Lisa A. Newman, MD, MPH	University of Michigan, Ann Arbor, MI	Surgical oncology
Cheryl L. Perkins, MD, RPH	Dallas, TX	Advocate/survivor
Donald A. Podoloff, MD	University of Texas MD Anderson Cancer Center, Houston, TX	Nuclear medicine and diagnostic radiology
Roderick R. Turner, MD	John Wayne Cancer Institute, Santa Monica, CA	Pathology
Donald L. Weaver, MD	University of Vermont College of Medicine and Vermont Cancer Center, Burlington, VT	Pathology

NOTE. American Society of Clinical Oncology staff: Sarah Temin, MSPH.
Abbreviation: PGIN, Practice Guidelines Implementation Network.