Original Investigation

Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer
The ACOSOG Z1071 (Alliance) Clinical Trial

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IMPORTANCE Sentinel lymph node (SLN) surgery provides reliable nodal staging information with less morbidity than axillary lymph node dissection (ALND) for patients with clinically node-negative (cN0) breast cancer. The application of SLN surgery for staging the axilla following chemotherapy for women who initially had node-positive cN1 breast cancer is unclear because of high false-negative results reported in previous studies.

OBJECTIVE To determine the false-negative rate (FNR) for SLN surgery following chemotherapy in women initially presenting with biopsy-proven cN1 breast cancer.

DESIGN, SETTING, AND PATIENTS The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial enrolled women from 136 institutions from July 2009 to June 2011 who had clinical T0 through T4, N1 through N2, M0 breast cancer and received neoadjuvant chemotherapy. Following chemotherapy, patients underwent both SLN surgery and ALND. Sentinel lymph node surgery using both blue dye (isosulfan blue or methylene blue) and a radiolabeled colloid mapping agent was encouraged.

MAIN OUTCOMES AND MEASURES The primary end point was the FNR of SLN surgery after chemotherapy in women who presented with cN1 disease. We evaluated the likelihood that the FNR in patients with 2 or more SLNs examined was greater than 10%, the rate expected for women undergoing SLN surgery who present with cN0 disease.

RESULTS Seven hundred fifty-six women were enrolled in the study. Of 663 evaluable patients with cN1 disease, 649 underwent chemotherapy followed by both SLN surgery and ALND. An SLN could not be identified in 46 patients (7.1%). Only 1 SLN was excised in 78 patients (12.0%). Of the remaining 525 patients with 2 or more SLNs removed, no cancer was identified in the axillary lymph nodes of 215 patients, yielding a pathological complete nodal response of 41.0% (95% CI, 36.7%-45.3%). In 39 patients, cancer was not identified in the SLNs but was found in lymph nodes obtained with ALND, resulting in an FNR of 12.6% (90% Bayesian credible interval, 9.85%-16.05%).

CONCLUSIONS AND RELEVANCE Among women with cN1 breast cancer receiving neoadjuvant chemotherapy who had 2 or more SLNs examined, the FNR was not found to be 10% or less. Given this FNR threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND.

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Axillary lymph node status is an important prognostic factor in breast cancer and is used to guide local, regional, and systemic treatment decisions. In patients with large primary tumors or involved lymph nodes, chemotherapy is often delivered preoperatively in order to assess the tumor's response to chemotherapy and to increase the likelihood of breast-conserving surgery. Residual axillary nodal disease is found in only 50% to 60% of patients initially presenting with clinical node-positive disease who receive neoadjuvant chemotherapy. Accurate determination of axillary involvement after chemotherapy is important; however, removing all axillary nodes to assess for residual nodal disease subjects many patients to the morbidity of surgery and, potentially, only a subset will benefit.

To avoid the complications associated with axillary lymph node dissection (ALND), it is preferable to identify nodal disease with the less invasive sentinel lymph node (SLN) surgical procedure, which results in less morbidity.[1] Sentinel lymph node surgery is considered reliable for identifying axillary nodal disease in women initially presenting with clinical node-negative (cN0) disease. False-negative results can occur when the SLNs do not contain cancer, but cancer is found in nodes obtained from ALND. False-negative rates (FNRs) for SLN surgery range from 0% to 20%[2-9] after chemotherapy in patients with cN0 disease, with a meta-analysis reporting an FNR of 12%.[10] Investigators from the the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial included both cN0 and cN1 disease and reported an SLN FNR of 10.7% after chemotherapy.[9] However, the use of SLN surgery following neoadjuvant chemotherapy for patients with cN1 disease has been questioned because the only available data has been from small series reporting FNRs ranging from 7% to 25%.[9,11]

ALND *axillary lymph node dissection*
FNR *false-negative rate*
pCR *pathologic complete response*
SLN *sentinel lymph node*

Anthracyclines and taxane-based chemotherapy regimens have been shown to eradicate nodal disease in approximately 30% to 40% of patients.[12] These patients would not be expected to benefit from ALND and may have complications from the procedure. In order to apply SLN surgery in this setting, an acceptably low FNR must be demonstrated. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial was designed to determine the FNR of SLN surgery after chemotherapy in women initially presenting with cN1 disease.

Methods

The phase 2 clinical trial was designed to determine the FNR for SLN surgery performed after neoadjuvant chemotherapy in women presenting with pathologically confirmed node-positive disease. The institutional review boards of all participating institutions approved this study, and written informed consent was obtained from each patient before study entry.

Eligibility and Exclusion Criteria

We enrolled women aged 18 years or older who (1) had histologically proven clinical stage T0 through T4, N1 through N2, M0 primary invasive breast cancer according to the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, sixth edition (**Table 1**), (2) had an Eastern Cooperative Oncology Group performance status of 0 or 1, (3) had completed or were planning to undergo neoadjuvant chemotherapy (the regimen was at the discretion of the patient's medical team), and (4) had prechemotherapy axillary nodal disease confirmed by fine-needle aspiration or core-needle biopsy. Patients with a history of prior ipsilateral axillary surgery, prior SLN surgery, or excisional lymph node biopsy for pathologic confirmation of axillary status were excluded. Patients were staged according to the AJCC staging system as cN1 (disease in movable axillary lymph nodes) or cN2 (disease in fixed or matted axillary lymph nodes).

Surgical Intervention and Nodal Evaluation

Breast cancer surgery was performed within 84 days after the completion of chemotherapy. After chemotherapy and within 4 weeks before surgery, patients underwent a physical examination and axillary ultrasonography. At surgery, patients had appropriate treatment of the primary tumor and underwent SLN surgery and then ALND.

Sentinel lymph node surgery allows surgeons to identify the first lymph node(s) along the lymphatic drainage pathway from the primary tumor in the breast to the axillary lymph node basin. It requires the injection of a radiolabeled colloid, blue dye (isosulfan blue or methylene blue), or a combination of these into the breast. The mapping agent is taken up by the breast lymphatics as they travel to the axillary nodes. If radiolabeled colloid is used, a gamma probe identifies radioactivity in the lymph nodes in the axilla. If blue dye is used, blue-stained lymphatic channels visualized during surgery are followed to lymph nodes where the blue dye accumulates. Additionally, the axilla is carefully palpated and any palpably abnormal lymph nodes are identified. Lymph nodes that are radioactive, blue, or palpably abnormal are considered SLNs and are resected and submitted for pathological analysis.

Sentinel lymph node mapping with both blue dye and radiolabeled colloid mapping agents was recommended to maximize the likelihood of SLN identification and to minimize the possibility of missing SLNs, which could result in a false-negative event. All SLNs were excised and submitted before the ALND was performed. The protocol required that at least 2 SLNs be resected. Each SLN was examined with hematoxylin-eosin staining, and positive SLNs were defined as those with metastases larger than 0.2 mm (per the AJCC staging system). Nodes removed at ALND were evaluated by hematoxylin-eosin staining using each institution's standard operating procedures.

Statistical Analysis

Our study was designed to evaluate the primary and secondary end points in the cN1 cohort independently of that in the

cN2 cohort. The primary aim was to examine the FNR of SLN surgery after chemotherapy when at least 2 SLNs were excised. A secondary aim was to determine the pathologic complete nodal response (pCR) rate wherein a nodal pCR is pathologically node-negative (pN0) on the basis of SLN surgery and ALND.

In the cN1 cohort, a Bayesian clinical trial design was chosen to determine whether the FNR was greater than 10%,[13,14] the rate expected for SLN surgery in women who initially present with clinically negative axillary lymph nodes. Assuming the number of women with negative SLN results after chemotherapy, X, has a binomial (n, θ) distribution, where θ is the probability of a false-negative SLN result and its prior distribution is a uniform (0,1) distribution, then the posterior distribution for θ is a β(x +1,n-x +1) distribution. The SLN FNR is considered too high if there is a greater than 95% chance that the FNR is greater than 10%. With a sample size of 300 patients, this translated to concluding that the SLN FNR is greater than 10% if 39 or more patients are found to have a false-negative SLN finding. The result of 10 000 simulations of this study design with the FNR set at 10% found that 5.3% of the simulated trials would incorrectly conclude that the FNR is greater than 10%. A 2-sided, 90% Bayesian credible interval (BCI) for the true FNR was constructed.

In an exploratory analysis, Fisher exact tests and multivariable logistic regression modeling with score statistics and likelihood ratio tests were used on the likelihood of a false-negative SLN finding. All tests were 2-sided.

In the cN2 cohort, it was anticipated that 43 women with cN2 disease would be enrolled who would have at least 2 SLNs examined after chemotherapy and have residual nodal disease. However, only 14 such women were enrolled, and a 95% binomial confidence interval for the FNR in this patient population was constructed.

A 95% binomial confidence interval was constructed for the pCR rate.

The database used for these analyses was locked May 1, 2013. Statistical analyses were carried out using SAS (SAS Institute Inc, version 9.2).

Results

Seven hundred fifty-six women with clinical stage T0 through T4, N1 through N2, M0 breast cancer who received neoadjuvant chemotherapy were enrolled from July 2009 to June 2011 from 136 institutions. Twenty-one women were ineligible, and 34 patients withdrew from the study before surgery (**Figure**). Patient, disease, and chemotherapy characteristics for the remaining 701 women are presented in Table 1 by clinical nodal stage prior to chemotherapy. A total of 663 women had cN1 disease, and 38 had cN2 disease.

The chemotherapy regimens varied, but the majority included an anthracycline and taxane (74.6%, Table 1). The duration of chemotherapy varied from 1 to 7 months (median, 4 months). Fifty-nine patients (8.4%) discontinued chemotherapy early because of disease progression (7 patients, 1.0%), intolerable adverse effects (42 patients, 6.0%), refusal (5 pa-

Table 1. Patient and Treatment Characteristics by Clinical Nodal Staging at Presentation[a]

Characteristics	No. (%) cN1 Cohort (n = 663)	No. (%) cN2 Cohort (n = 38)
Age, y		
18-39	120 (18.1)	4 (10.5)
40-49	213 (32.1)	15 (39.5)
50-59	197 (29.7)	10 (26.3)
60-69	112 (16.9)	5 (13.2)
≥70	21 (3.2)	4 (10.5)
Race/ethnicity		
White	537 (81.0)	28 (73.7)
Black or African American	95 (14.3)	5 (13.2)
Asian	18 (2.7)	1 (2.6)
American Indian or Alaska Native	2 (0.3)	1 (2.6)
Not reported	11 (1.6)	3 (7.9)
BMI		
<25.0	187 (28.2)	9 (23.7)
≥25.0	475 (71.6)	28 (73.7)
Unknown	1 (0.2)	1 (2.6)
Eastern Cooperative Oncology Group performance status		
0	536 (80.8)	26 (68.4)
1	127 (19.2)	12 (31.6)
Smoking status		
Current	81 (12.2)	4 (10.5)
Never	451 (68.0)	30 (78.9)
Past	104 (15.7)	4 (10.5)
Not stated	27 (4.1)	0
Concurrent conditions		
Diabetes	53 (8.0)	4 (10.5)
Peripheral vascular disease	3 (0.4)	1 (2.6)
Arthritis	44 (6.6)	4 (10.5)
Cardiac disease	169 (25.5)	10 (26.3)
Clinical T category at diagnosis[b]		
T0/Tis	5 (0.8)	2 (5.3)
T1	86 (13.0)	5 (13.2)
T2	372 (56.1)[c]	13 (34.2)
T3	175 (26.4)	10 (26.3)
T4	25 (3.8)	8 (21.1)
Approximated subtype		
ERBB2-positive (formerly *HER2*)	197 (29.7)	12 (31.6)
Hormone receptor–positive/ *ERBB2*-negative	301 (45.4)	14 (36.8)
Triple receptor–negative	156 (23.5)	10 (26.3)
Insufficient information to classify/ no invasive breast tumor/ prior breast surgery	9 (1.4)	2 (5.3)
Tumor histology		
IDC	590 (89.0)	30 (79.0)
ILC	37 (5.6)	1 (2.6)
Mix of IDC and ILC	11 (1.7)	0
Invasive carcinoma, other	20 (3.0)	5 (13.2)
DCIS	2 (0.3)	0
No breast disease, stage T0	3 (0.5)	2 (5.3)

(continued)

Table 1. Patient and Treatment Characteristics by Clinical Nodal Staging at Presentation[a] (continued)

Characteristics	No. (%) cN1 Cohort (n = 663)	No. (%) cN2 Cohort (n = 38)
Type of axillary lymph node biopsy		
Fine-needle aspiration	259 (39.1)	13 (34.2)
Core-needle biopsy	404 (60.9)	25 (65.8)
Clip placed in axilla		
Yes	214 (32.3)	16 (42.1)
No	448 (67.6)	22 (57.9)
Not stated	1 (0.2)	0
Neoadjuvant chemotherapy regimen		
Anthracycline and a taxane	499 (75.3)	24 (63.2)
Anthracycline	41 (6.2)	3 (7.9)
Taxane	112 (16.9)	10 (26.3)
No anthracycline and no taxane	11 (1.7)	1 (2.6)
Chemotherapy completed	609 (91.9)	33 (86.8)
Reason chemotherapy discontinued		
Disease progression	6 (0.9)	1 (2.6)
Intolerable adverse effects	38 (5.7)	4 (10.5)
Refusal	5 (0.7)	0
Lack of tumor response	3 (0.4)	0
Physician discretion	1 (0.2)	0
Desire for alternative therapy	1 (0.2)	0
Findings on axilla after chemotherapy		
No palpable adenopathy	556 (83.9)	26 (68.4)
Palpable lymph nodes	76 (11.5)	8 (21.1)
Fixed or matted lymph nodes	2 (0.3)	2 (5.3)
Not reported	29 (4.4)	2 (5.3)
Type of breast surgery after chemotherapy		
Partial mastectomy	266 (40.1)	11 (28.9)
Total mastectomy	395 (59.6)	25 (65.8)
None	2 (0.3)	2 (5.3)
Type of axillary surgery		
SLN	2 (0.3)	0
SLN with no SLN identified and ALND	46 (6.9)	4 (10.5)
SLN with SLN identified and ALND	603 (91.0)	34 (89.5)
ALND	12 (1.8)	0

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; SLN, sentinel lymph node.

[a] cN1 indicates disease in movable axillary lymph nodes; and cN2, disease in fixed or matted axillary lymph nodes.

[b] T0 indicates no evidence of disease in the breast; T1, breast tumor size 2 cm or less; T2, breast tumor more than 2 cm but at most 5 cm; T3, breast tumor size larger than 5 cm; and T4, tumor extension to chest wall or skin.

[c] One patient underwent a partial mastectomy prior to chemotherapy.

tients, 0.7%), lack of tumor response (3 patients, 0.4%), physician discretion (1 patient, 0.1%), or a desire for alternative therapy (1 patient, 0.1%).

After completion of chemotherapy, clinical examination of the axilla revealed no palpable lymphadenopathy in 582 patients (83.0%), palpable nodes in 84 patients (12.0%), and fixed or matted nodes in 4 patients (0.6%). Results of palpation were not reported in 31 patients (4.4%).

Of the 701 evaluable women, 2 women (0.3%) underwent SLN surgery only, 687 women (98.0%) underwent both SLN surgery and ALND, and 12 (1.7%) underwent ALND only.

SLN Surgery

Of the 689 women who underwent SLN surgery (**Table 2**), 28 (4.1%) had mapping performed with blue dye only, 116 (16.8%) had mapping with radiolabeled colloid only, and 545 (79.1%) had mapping with both blue dye and radiolabeled colloid.

At least 1 SLN was detected in 639 (92.7% [95% CI, 90.5%-94.6%]) of these 689 women. Rates of detection of at least 1 SLN were 92.9% (n = 605; 95% CI, 90.7%-94.8%) in the 651 patients with cN1 disease and 89.5% (n = 34; 95% CI, 75.2%-97.1%) in the 38 patients with cN2 disease.

FNR in Women With cN1 Disease and 2 or More SLNs Examined

There were 525 patients with cN1 disease who had at least 2 SLNs excised and went on to complete ALND. Pathologic examination of the SLNs and nodes removed at ALND found no residual nodal disease in 215 of these patients, yielding a nodal pCR rate of 41.0% (95% CI, 36.7%-45.3%). Among the remaining 310 patients, residual nodal disease was confined to the SLNs in 108 patients (20.6%), confined to the nodes removed on ALND in 39 patients (7.4%), and present in nodes from both procedures in 163 patients (31.1%). Thus, 39 of the 310 patients with residual nodal disease had a false-negative SLN finding, an FNR of 12.6% (90% BCI, 9.85%-16.05%).

Bivariable analyses found that the likelihood of a false-negative SLN finding was significantly decreased when the mapping was performed with the combination of blue dye and radiolabeled colloid (P = .05; FNR, 10.8% combination vs 20.3% single agent) and by examination of at least 3 SLNs (P = .007; FNR, 9.1% for ≥3 SLNs vs 21.1% for 2) (**Table 3**). Multivariable logistic modeling revealed that, once the number of SLNs examined (2 vs ≥3) was accounted for, no other factors made a significant contribution in explaining the variability in likelihood of a false-negative SLN finding.

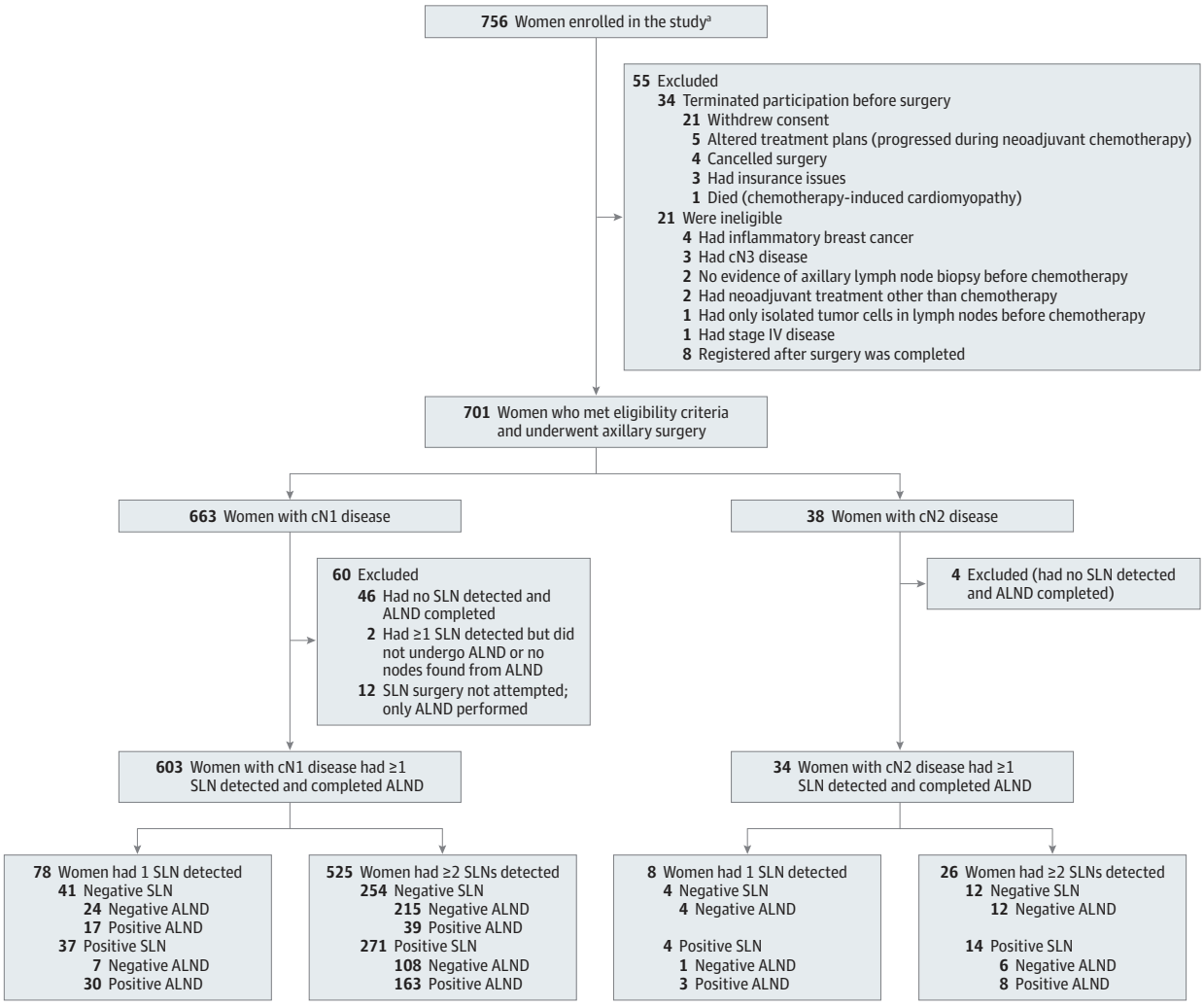
Women With cN2 Disease and at Least 2 SLNs Examined

Among the 26 women with cN2 disease with at least 2 SLNs excised followed by ALND, 12 patients had no residual nodal disease, resulting in a pCR rate of 46.1% (95% CI, 26.6%-66.6%). Fourteen patients had residual nodal disease either confined to the SLNs (6 patients) or present in both SLNs and nodes removed on ALND (8 patients), yielding an FNR of 0% (95% CI, 0%-23.2%).

Discussion

This multicenter trial showed that the FNR of SLN surgery after neoadjuvant chemotherapy in patients with cN1 breast cancer and at least 2 SLNs identified at the time of surgery

Figure. Flow of Women Through the Study



[a]The number of women approached to consider enrollment into this study is unknown. ALND indicates axillary lymph node dissection; and SLN, sentinel lymph node.

was 12.6%, higher than the prespecified threshold of 10%. This threshold was considered acceptable based on prior studies of SLN surgery reporting a 10% to 12% FNR following chemotherapy in patients with cN0 disease.[10]

Although our findings suggest that surgeons cannot reliably detect all axillary lymph node metastases in patients with cN1 breast cancer following chemotherapy by SLN procedures, we did identify important factors influencing the likelihood of a false-negative SLN. The FNR was significantly lower when a dual-agent mapping technique (10.8%) vs a single-agent mapping (20.3%; $P = .05$) technique was used. The FNR with dual-agent mapping reported in this study is similar to the findings from the NSABP B-27 trial, wherein investigators reported an FNR of 9.3% with dual-agent mapping predominantly in patients with cN0 disease, but some with cN1 disease.[14] After chemotherapy, the axilla often has more fibrosis, making evaluation of lymphatic drainage and surgical dissection more challenging. Using 2 mapping agents with different molecular sizes and transit times is an important surgical standard that should be adhered to for SLN surgery after chemotherapy.

Our study also found that the FNR was lower when 3 or more SLNs are evaluated vs only 2 SLNs being evaluated. In the NSABP B-27 trial, this issue was not addressed. The NSABP B-32 trial, in which SLN surgery was performed before any chemotherapy, reported that there was a significant decrease in the FNR as more SLNs were resected: 18% with 1 SLN resected, 10% with 2 SLNs resected, and 7% with 3 SLNs resected.[15] Similarly, Hunt and coauthors[16] showed that the removal of fewer than 2 SLNs was associated with a higher FNR in patients with cN0 disease undergoing SLN surgery after chemotherapy. As the accuracy of any sampling test is dependent on the amount of material sampled, these results are not surprising.

Table 2. Details of Sentinel Lymph Node Surgery

Variable	No. (%) cN1 (n = 651)	cN2 (n = 38)
Mapping agent used		
Blue dye	25 (3.8)	3 (7.9)
Radiolabeled colloid	109 (16.7)	7 (18.4)
Both	517 (79.4)	28 (73.7)
Timing of radiolabeled colloid injection		
Day before surgery	160 (24.6)	5 (13.2)
Morning of surgery	466 (71.6)	30 (78.9)
Not used	25 (3.8)	3 (7.9)
Injection sites		
Subareolar/periareolar	404 (62.1)	31 (81.6)
Peritumoral	56 (8.6)	1 (2.6)
Intradermal	17 (2.6)	2 (5.3)
Multiple sites	147 (22.6)	2 (5.3)
Not specified	27 (4.1)	2 (5.3)
No. of SLNs examined		
0	46 (7.1)	4 (10.5)
1	78 (12.0)	8 (21.1)
2	155 (23.8)	10 (26.3)
3	148 (22.7)	6 (15.8)
4	90 (13.8)	5 (13.2)
≥5	134 (20.6)	5 (13.2)

Abbreviation: SLN, sentinel lymph node.

A shortcoming of this study is that patients who had node-positive disease prior to planned chemotherapy could be enrolled before, during, or after chemotherapy regardless of the type or length of therapy, reason for discontinuing chemotherapy, or nodal response after chemotherapy (based on physical examination or axillary ultrasound). More appropriate candidates for SLN surgery may have been patients with the highest likelihood of nodal response and lowest likelihood of residual nodal disease and those with normalization of nodal architecture on ultrasonography. As such, patients with significant residual nodal disease or poor clinical or radiologic response to chemotherapy are most likely poor candidates for SLN surgery. Until further data are available, we recommend that SLN surgery after chemotherapy not be performed in patients with clinically evident residual nodal disease or poor response to chemotherapy.

Conclusion

In summary, our trial found that both the use of dual-agent mapping and recovery of more than 2 SLNs were associated with a lower likelihood of false-negative SLN findings. Among women with cN1 breast cancer who received neoadjuvant chemotherapy and had 2 or more SLNs examined, the FNR was 12.6% (90% BCI, 9.85%-16.05%) with SLN surgery and exceeded the prespecified threshold of 10%. Given this accept-

Table 3. Factors Affecting the Likelihood of a False-Negative Sentinel Lymph Node Finding in the 310 Women With cN1 Disease at Presentation, 2 or More SLNs Examined, and Residual Nodal Disease After Neoadjuvant Chemotherapy

	False-Negative SLN Findings, No. (Total)	FNR (95% CI), %	Fisher Exact Test, *P* Value
Age, y			
18.0-49.9	20 (150)	13.3 (8.3-19.8)	.73
≥50.0	19 (160)	11.9 (7.3-17.9)	
BMI			
≥25.0	25 (227)	11.0 (7.3-15.8)	.18
<25.0	14 (83)	16.9 (9.5-26.7)	
Clinical T category prior to chemotherapy			
Tis, T0, T1, or T2	32 (225)	14.2 (9.9-19.5)	.18
T3 or T4	7 (85)	8.2 (3.4-16.2)	
Chemotherapy duration, mo			
≤4.0	20 (201)	10.0 (6.2-15.0)	.07
≥4.1	19 (109)	17.4 (10.8-25.9)	
Palpable, fixed, or matted nodes after chemotherapy[a]			
Yes	10 (52)	19.2 (9.6-32.5)	.17
No	28 (247)	11.3 (7.7-16.0)	
Mapping agents used			
Single	12 (59)	20.3 (11.0-32.8)	.05
Dual	27 (251)	10.8 (7.2-15.3)	
Multiple injection sites[b]			
Yes	5 (70)	7.1 (2.4-15.9)	.21
No	30 (225)	13.3 (9.2-18.5)	
No. of SLNs examined			
2	19 (90)	21.1 (13.2-31.0)	.007
≥3	20 (220)	9.1 (5.6-13.7)	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; FNR, false-negative rate; SLN, sentinel lymph node.

[a] Not reported in 11 patients.

[b] Not reported in 15 patients.

ability threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND in this patient population.

ARTICLE INFORMATION

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