ONLINE FIRST

Long-term Outcome of Patients Managed With Sentinel Lymph Node Biopsy Alone for Node-Negative Invasive Breast Cancer

Nimmi S. Kapoor, MD; Myung-Shin Sim, DrPH; Jennifer Lin, MD; Armando E. Giuliano, MD

Objective: To examine the long-term outcome of patients with early breast cancer with hematoxylin-eosin–negative sentinel lymph nodes (SLNs) who did not undergo completion axillary lymph node dissection.

Design, Setting, and Patients: Patients with invasive breast cancer surgically treated between May 1, 1995, and December 31, 2002, with SLN biopsy alone without axillary lymph node dissection who had hematoxylin-eosin–negative SLNs were identified.

Main Outcome Measures: Patient and tumor characteristics, adjuvant treatment, disease recurrence, and survival were recorded. A multivariable analysis model was used to identify significant variables associated with disease-free survival and overall survival.

Results: A total of 811 patients were included, with a median follow-up of 103.1 months (range, 12.2-182.8 months). The mean patient age was 57.8 years (range, 26-91 years), the mean tumor size was 1.5 cm (range, 0.1-7.5 cm), and the median number of SLNs obtained was 2 (range, 1-8). Seventy-six patients (9.4%) developed disease recurrence; there were 2 patients (0.2%) with isolated axillary recurrences, 40 (4.9%) with local recurrences, 4 (0.5%) with local and regional recurrences, 22 (2.7%) with distant recurrences, and 8 (1.0%) with both local and distant recurrences. The median time to recurrence was 57.2 months (range, 3.1-163.3 months), with 5-year and 10-year disease-free survival rates of 95.1% and 89.9%, respectively. One hundred one patients (12.5%) died; only 15 (1.8%) had distant metastatic disease at the time of death. Patients were significantly more likely to have disease recurrence if they had high-grade tumors ($P=.004$). Older age and larger tumor size were significant predictors of worse overall survival on multivariate analysis ($P<.001$ and $P=.01$, respectively).

Conclusions: This study reports the long-term follow-up of patients with breast cancer and hematoxylin-eosin–negative, tumor-free SLNs, showing a remarkably low axillary recurrence of 0.2% and high disease-free survival. Long-term results of SLN biopsy alone are excellent, and the addition of immunohistochemistry analysis does not contribute to survival.

Arch Surg. 2012;147(11):1047-1052. Published online July 16, 2012. doi:10.1001/archsurg.2012.1563

Author Affiliations:
Departments of Breast Surgical Oncology (Drs Kapoor and Lin) and Biostatistics (Dr Sim), John Wayne Cancer Institute, Santa Monica, and Cedars-Sinai Medical Center (Drs Kapoor and Lin) and Departments of Surgery and Surgical Oncology, Samuel Oschin Comprehensive Cancer Institute (Dr Giuliano), Los Angeles, California.

THE MOST USEFUL PROGNOSTIC factor for patients with breast cancer is the presence or absence of lymph node metastasis.[1] Sentinel lymph node (SNL) biopsy (SLNB) has replaced axillary lymph node dissection (ALND) as the standard method of evaluating patients with early breast cancer and clinically negative axilla. The efficacy and safety of SLNB have been confirmed to be equal to those of ALND in randomized controlled trials.[2-4] The use of SLNB substantially decreases the risk of morbidity from pain, numbness, and lymphedema[5-7] and permits more careful examination of the SLNs.[8-10]

One of the consequences of this more careful evaluation of SLNs is a stage migration of disease,[10,11] with more patients being identified as having micrometastatic nodal disease burden, often leading to more patients undergoing adjuvant systemic therapy. The importance and predictive power of micrometastasis, however, have been controversial. Recently, a number of studies evaluating the prognostic significance of micrometastasis and isolated tumor cells (ITCs) in SLNs have shown that these SLNs with limited burden of disease have a minimal effect on disease-free survival (DFS) and overall survival (OS).[11-14] It has been further suggested that immunohistochemistry (IHC) analysis of SLNs be abandoned completely and that evaluation of SLNs be done by hematoxylin-eosin (HE) staining alone.[12] However, long-term survival data of patients with HE-negative SLNs are limited. This study was undertaken to evaluate the 10-year DFS and OS of patients with tumor-free SLNs with HE staining, regardless of IHC status, managed without ALND.

Table 1. Study Characteristics

Variable	Value
Patient age, mean (range), y	57.8 (26-91)
Tumor size, mean (range), cm	1.5 (0.1-7.5)
SLNs examined, median (range), No.	2 (1-8)
Tumor histology, No. (%)	
IDC	677 (83.5)
ILC	86 (10.6)
Mixed	48 (5.9)
Grade, No. (%)	
Low	284 (35.0)
Intermediate	305 (37.6)
High	201 (24.8)
Unknown	21 (2.6)
Estrogen receptor, No. (%)	
Positive	591 (72.9)
Negative	115 (14.2)
Unknown	105 (12.9)
Progesterone receptor, No. (%)	
Positive	461 (56.8)
Negative	238 (29.4)
Unknown	112 (13.8)
HER2/neu, No. (%)	
Positive	67 (8.3)
Negative	366 (45.1)
Unknown	378 (46.6)
Method of nodal evaluation, No. (%)[a]	
HE and IHC	532 (65.6)
HE only	279 (34.4)
IHC findings of SLNs, No. (%) (n=532)	
Negative	571 (88.5)
Positive	61 (11.5)
Surgery, No. (%)	
Breast conservation	760 (93.7)
Mastectomy	51 (6.3)
Hormone therapy, No. (%)	
Yes	380 (46.9)
No	423 (52.2)
Unknown	8 (1.0)
Chemotherapy, No. (%)	
Yes	216 (26.6)
No	586 (72.3)
Unknown	9 (1.1)

Abbreviations: HE, hematoxylin-eosin; HER2/neu, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; IHC, immunohistochemistry; ILC, invasive lobular carcinoma; SLNs, sentinel lymph nodes.

[a] Node positivity was defined using guidelines from the American Joint Commission on Cancer *AJCC Cancer Staging Manual*, seventh edition[17] (see "Methods").

METHODS

Patients with invasive breast cancer and clinically negative axilla surgically treated at the Saint John's Health Center in conjunction with the John Wayne Cancer Institute between May 1, 1995, and December 31, 2002, were identified from a prospectively maintained database. Patients were included if they had a tumor-free SLNB specimen that was negative with routine HE staining and negative or positive with IHC analysis. Patients were excluded if they underwent a completion ALND.

All patients underwent intraoperative SLNB as described previously.[15] Histopathologic evaluation of each SLN has been described.[16] Briefly, each SLN was bisected and blocked for permanent sectioning and was stained with standard HE; if negative, 6 to 8 sections of the SLN were submitted for further HE staining and IHC analysis. In a minority of patients, only HE staining was performed on multiple sections as patients were subject to research protocols prohibiting the use of IHC analysis.

During the study period, the standard of care for all patients undergoing breast-conserving therapy was whole-breast irradiation with standard tangents; partial breast irradiation was not in practice.

Nodal metastasis was defined using current guidelines from the American Joint Commission on Cancer *AJCC Cancer Staging Manual*, seventh edition.[17] The ITCs are defined as a 0.2-mm or smaller deposit of tumor cells in a lymph node; micrometastasis is larger than 0.2 mm but smaller than 2.0 mm; and macrometastasis is larger than 2.0 mm. Both micrometastasis and macrometastasis are typically seen with HE staining, whereas ITCs are usually only seen with IHC staining. Because all patients with HE-negative SLNs were included, patients with both pN0(i–) and pN0(i+) SLNs were included.

Recurrences were defined as axillary if only axillary disease was identified, as local for ipsilateral breast tumor recurrence (IBTR) or chest wall recurrence after mastectomy alone, as breast and axilla if both ipsilateral breast and axilla were simultaneously involved with tumor recurrence, and as distant for all other nonbreast, nonaxilla organ sites. Patients with either simultaneous or sequential local and distant metastasis were counted only once as local *and* distant disease recurrence.

Clinical variables were extracted from our registered cancer database and from patients' records. Variables included patient age, tumor size, histologic type, grade, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 (HER2/neu) status, number of SLNs evaluated, method of nodal evaluation (ie, both HE staining and IHC analysis vs HE staining only), surgical treatment (breast-conserving surgery [BCS] vs mastectomy), and adjuvant systemic treatment. The HER2/neu status was not routinely determined during the first half of the study period; thus, this data point is not available for a number of patients. The US Social Security Death Index was reviewed to confirm deaths. The DFS, OS, and disease-specific survival were calculated using the Kaplan-Meier method, and univariate and multivariate analyses were performed using the log-rank test and Cox regression analysis.

RESULTS

A total of 811 patients with HE-negative tumor-free SLNs managed without completion ALND were included in this study. Patient and tumor characteristics are listed in **Table 1**. Of 532 patients with SLNs evaluated by both HE staining and IHC analysis, 61 (11.5%) had IHC-positive SLNs. For the other 279 patients (34.4%), SLNs were evaluated with HE staining only. Most patients underwent BCS for T1, estrogen receptor–positive, invasive ductal carcinomas. The mean and median numbers of SLNs removed were 2.2 and 2, respectively. Adjuvant systemic therapy given is listed in Table 1. In total, 491 patients (60.5%) received some form of adjuvant systemic therapy. Of the 61 patients with IHC-positive SLNs, 41 (67.2%) received adjuvant systemic therapy; 20 (32.8%) received hormone therapy alone, 9 (14.8%) received chemotherapy alone, and 12 (19.7%) received a combination of hormone therapy and chemotherapy. **Table 2** shows the breakdown of adjuvant systemic therapy administration based on SLN

Table 2. Adjuvant Systemic Therapy by Method of Sentinel Lymph Node Evaluation

Systemic Treatment	No. (%)		
	HE and IHC		
	IHC Negative (n=571)	IHC Positive (n=61)	HE Only (n=279)
Hormone therapy	195 (34.2)	32 (52.5)	153 (54.8)
Chemotherapy	99 (17.3)	21 (34.4)	96 (35.4)
Any adjuvant systemic therapy	252 (44.1)	41 (67.2)	198 (71.0)

Abbreviations: HE, hematoxylin-eosin; IHC, immunohistochemistry.

Table 3. Recurrence Patterns

Type of Recurrence	No. (%)
Breast or chest wall only	40 (4.9)
Axilla alone	2 (0.2)
Breast with axilla	4 (0.5)
Distant	22 (2.7)
Local and distant	8 (1.0)
Total	**76 (9.4)**

evaluation. More patients who had IHC-positive SLNs had adjuvant systemic therapy; however, those in whom the SLNs were not examined with IHC analysis had rates of adjuvant systemic therapy similar to those who had IHC-positive SLNs.

The median follow-up time for patients was 103.1 months (range, 12.2-182.8 months). There were 76 recurrences (9.4%). The median time to recurrence was 57.2 months (range, 3.1-163.3 months). **Table 3** lists types of recurrences. Most recurrences were local. Two patients undergoing mastectomy had chest wall recurrences and 42 patients undergoing BCS had IBTR. Four of these patients also had simultaneous axillary disease. Of the 811 patients, there were only 2 isolated axillary recurrences (0.2%), at 16 and 99 months from initial breast cancer diagnosis. Both of these patients had negative SLNs evaluated with HE staining only, and neither patient had nodes evaluated with IHC analysis. There were no supraclavicular or internal mammary node recurrences. Thirty patients (3.7%) developed distant disease either with (8 patients [1.0%]) or without (22 patients [2.7%]) a simultaneous local recurrence. One hundred one patients (12.5%) died in the study. Of the patients who died, 15 had distant disease at the time of death and died at a median of 46.9 months (range, 11.3-125.0 months). The remaining 86 patients who died in the study period either died of other documented causes or died without evidence of metastatic disease. Thus, the observed rate of death due to breast cancer from this study is 1.8% (15 of 811 patients). The 5- and 10-year OS, DFS, and estimated disease-specific survival are listed in **Table 4**. The 10-year DFS was 89.9% and the 10-year disease-specific survival was 97.7%. **Figure 1** shows the Kaplan-Meier curves for survival.

Table 5 shows the univariate analysis for DFS and OS. On univariate analysis, older age and larger tumor

Table 4. Rates of 5- and 10-Year OS, DFS, and DSS

Follow-up, y	% (95% CI)		
	OS	DFS	DSS
5	94.6 (92.8-96.0)	95.1 (93.3-96.4)	99.0 (98.0-99.5)
10	85.4 (82.0-88.1)	89.9 (87.1-92.2)	97.7 (96.0-98.7)

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival.

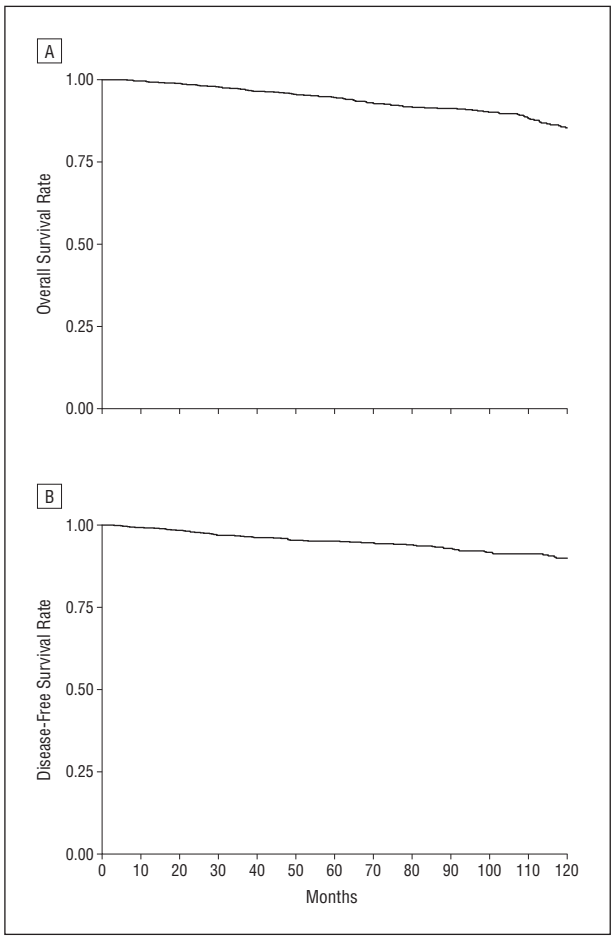

Figure 1. Kaplan-Meier curve of overall survival (A) and disease-free survival (B).

size were predictors of worse 10-year OS ($P<.001$ and $P=.01$, respectively), while receiving chemotherapy correlated with improved OS ($P=.03$). On multivariate analysis, older patient age, larger tumor size, and mastectomy were significant predictors of worse OS (**Table 6**). For the 10-year DFS, higher histologic tumor grade was the only variable predictive of worse DFS on both univariate and multivariate analyses (Table 5 and Table 6). **Figure 2** shows the Kaplan-Meier DFS by tumor grade.

COMMENT

This study reports the long-term follow-up of a large group of patients with tumor-free HE-negative SLNs. The 10-year DFS is excellent at 89.9%, and only 2 patients (0.2%)

Table 5. Univariate Analysis for 10-Year OS and DFS

Factor	10-y OS		10-y DFS	
	P Value	HR (95% CI)	*P* Value	HR (95% CI)
Age	<.001	1.06 (1.04-1.08)	.27	0.99 (0.97-1.01)
Tumor size	.01	1.02 (1.004-1.04)	.24	1.01 (0.99-1.03)
Histology				
IDC vs ILC	.83	0.90 (0.37-2.24)	.44	0.70 (0.28-1.74)
IDC vs mixed	.81	1.08 (0.56-2.10)	.57	0.71 (0.22-2.27)
Grade				
Low vs intermediate	.91	1.03 (0.62-1.69)	.004	3.00 (1.42-6.33)
Low vs high	.47	1.22 (0.71-2.10)	<.001	3.94 (1.82-8.52)
IHC positive	.54	0.79 (0.38-1.66)	.57	1.41 (0.43-4.57)
ER positive	.53	0.84 (0.48-1.47)	.49	0.79 (0.41-1.53)
PR positive	.87	1.04 (0.66-1.65)	.87	0.96 (0.56-1.64)
HER2/neu positive	.22	0.56 (0.22-1.40)	.85	1.08 (0.48-2.43)
BCS (vs mastectomy)	.16	0.59 (0.28-1.22)	.18	0.56 (0.24-1.30)
Chemotherapy	.03	0.52 (0.29-0.92)	.34	1.30 (0.76-2.21)
Hormone therapy	.35	0.82 (0.53-1.25)	.92	1.02 (0.62-1.68)
Any adjuvant therapy	.21	0.76 (0.50-1.16)	.55	1.17 (0.69-1.98)

Abbreviations: BCS, breast-conserving surgery; DFS, disease-free survival; ER, estrogen receptor; HER2/neu, human epidermal growth factor receptor 2; HR, hazard ratio; IDC, invasive ductal carcinoma; IHC, immunohistochemistry; ILC, invasive lobular carcinoma; PR, progesterone receptor; OS, overall survival.

Table 6. Multivariate Analysis for 10-Year OS and DFS Using Cox Regression Model

Variable	10-y OS		10-y DFS	
	P Value	HR (95% CI)	*P* Value	HR (95% CI)
Age	<.001	1.07 (1.05-1.08)		
Tumor size	.01	1.02 (1.00-1.03)		
Grade				
2 vs 1			.004	3.00 (1.42-6.35)
3 vs 1			<.001	3.94 (1.79-8.68)
Breast conservation	.02	0.42 (0.20-0.89)		

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

had isolated axillary recurrence at a median follow-up of 8.6 years. The median time to any disease recurrence was 4.8 years, showing the necessity of long-term follow-up for patients with node-negative breast cancer. These results are comparable, if not superior, to those given in the updated overview meta-analysis of 17 randomized controlled trials. Of the 7287 node-negative patients (pN0) included, the 10-year recurrence rate of patients treated with BCS and radiotherapy was 15.6%.[18] This meta-analysis also emphasized the need for such long-term follow-up as many distant recurrences will occur as late as 10 years after the primary breast cancer diagnosis.

The objective of this study was to take the information given from 2 contemporary large trials, NSABP Protocol B-32 (B-32) and American College of Surgeons Oncology Group Z0010 (Z0010),[2,12] which both evaluate the prognostic significance of occult nodal metastasis and report excellent 5-year DFS and OS rates of early breast cancer with HE-negative SLNs, and expand this to the 10-year DFS and OS of a large cohort of patients with HE-negative SLNs who were surgically treated at a single

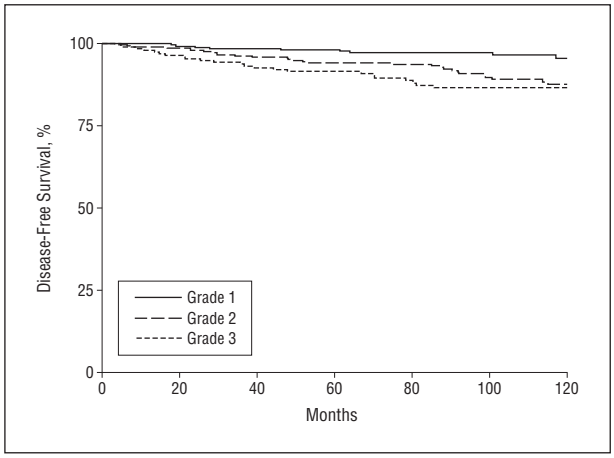

Figure 2. Kaplan-Meier plot of disease-free survival by tumor grade.

institution. This would ideally capture the majority of late events and provide further information on survival data for patients with tumor-free SLNs managed without ALND.

The B-32 trial was a randomized controlled trial of 5611 patients with invasive breast cancer and clinically negative axilla randomized to SLNB with ALND (group 1) vs SLNB and ALND only if the SLN was positive (group 2).[2] Treating physicians were blinded to results of IHC examination of SLNs and were only given the results of HE examination of SLNs. The trial was designed to detect a 2% survival difference at 5 years. At a mean follow-up of 95.6 months for the 3986 patients with tumor-free SLNs, 309 deaths were reported (140 of 1975 patients [7.1%] in group 1 and 169 of 2011 patients [8.4%] in group 2), for an unadjusted hazard ratio of 1.20 (95% CI, 0.96-1.50; *P*=.12). The 5-year OS rates for groups 1 and 2 were 96.4% and 95.0%, respectively, and the 8-year OS estimates were also high at 91.8% and 90.3%, respectively. This is very similar to the 5-year and 10-year OS rates of 94.6% and 85.4%, respectively, reported in the current study. These findings reinforce the excellent OS of patients with tumor-free SLNs managed without ALND.

Likewise, disease recurrence reported in B-32 was no different between group 1 (315 of 1975 patients [15.9%]) and group 2 (336 of 2011 patients [16.7%]), with the unadjusted hazard ratio of 1.05 (95% CI, 0.90-1.22; *P*=.54). The 5-year DFS rates for groups 1 and 2 were 89.0% and 88.6%, respectively, and the 8-year estimates were 82.4% and 81.5%, respectively. The B-32 trial included second (nonbreast cancers) and contralateral breast cancers as events captured for DFS, whereas this study did not.

Of all types of disease recurrences, the most scrutinized for both the current study and B-32 will be of axillary failures because patients did not undergo ALND. The rate of isolated axillary recurrences in this study was very low at 0.2% and was similar to that of group 2 in B-32 at 0.7% (14 of 2011 patients). More importantly, neither rate was significantly different from the 0.4% rate (8 of 1975 patients) of axillary recurrences in group 1 patients who underwent ALND. Unlike IBTR with simultaneous axillary disease, isolated axillary recurrences represent true failures of SLNB where disease in the axilla was left behind and not treated with surgical

removal, irradiation, and/or adjuvant therapy at initial treatment. Patients who have local recurrence with axillary disease could have axillary metastasis from their recurrence or possibly from disease left behind untreated from their primary cancer, but this will be largely unknown. Most studies will include IBTR with axillary recurrence as local recurrence. Nonetheless, in this study, only 4 patients had IBTR with axillary recurrence, giving a total 0.7% rate of any axillary disease recurrence, further supporting the efficacy of SLNB alone for patients with HE-negative SLNs.

Survival data from patients with HE-negative SLNs in B-32 were then evaluated in a separate report on the basis of occult metastasis detected by IHC analysis and multiple sections.[13] Of 3887 patients with HE-negative SLNs reevaluated to assess for occult metastasis, 15.9% of patients had occult nodal disease; 11.1% were ITCs. The B-32 trial found a small but statistically significant 1.2% decrease in the 5-year OS for patients with occult metastasis ($P=.03$). Similarly, there was a statistically significant 2.8% decrease in the 5-year DFS for patients with occult metastasis ($P=.02$). Not surprisingly, the hazard ratio for all survival outcomes decreased with a smaller burden of occult metastasis; for ITCs it was only 1.18, whereas for micrometastasis it was 1.38. The authors concluded that while a survival difference associated with the presence of occult metastasis existed, the clinical relevance of such a difference benefit was questionable.

On the other hand, Z0010, an observational study designed to evaluate the prognostic significance of occult metastasis in both SLNs and bone marrow, did not find a statistically significant difference in OS or recurrence between patients with IHC-positive SLNs and IHC-negative SLNs.[12] Similar to the current study and B-32, Z0010 reported 5-year OS rates of 95.1% for IHC-positive SLNs and 95.7% for IHC-negative SLNs. Again, the current study expands on the 6.3-year median follow-up of Z0010 and emphasizes the excellent outcome of patients with HE-negative SLNs, regardless of IHC positivity, managed without ALND.

In both B-32 and Z0010, treating clinicians were blinded to results of IHC staining of SLNs, and evaluation of SLNs for occult disease took place in a centralized laboratory. Patient selection for adjuvant systemic therapy was not biased by information from IHC testing of SLNs. Nonetheless, a majority of patients in both studies received adjuvant systemic therapy: 84.2% in B-32 and 83.3% in Z0010. In the current study, treating physicians were not blinded to the results of SLN evaluation with IHC and could have been biased by this finding. This could theoretically have an impact on survival benefit; however, only 7.5% of the study population had known, positive IHC staining results from their SLNs. Of those patients with IHC-positive SLNs, 67.2% received adjuvant systemic therapy, similar to that of patients with unknown IHC nodal status at 71.0%. While patients with IHC-positive SLNs were treated with adjuvant systemic therapy more often than those with IHC-negative SLNs, the observation that patients whose SLNs were not examined with IHC were not treated differently than those with IHC-positive SLNs suggests that the IHC-detected metastasis did not contribute to overall management. These results again are similar to those of B-32 and Z0010 as the treating physicians of patients with SLNs who only have HE staining results available are in effect blinded to the results of IHC analysis, yet are still treating patients no differently from those with IHC-positive SLNs. On the other hand, only 44.1% of patients with IHC-negative SLNs received adjuvant systemic therapy. It is possible that lack of knowledge of IHC status of the SLN leads physicians to treat their patients as though they might have occult metastasis, accounting for these differences in adjuvant therapy, or, more likely, that other tumor factors contribute to the detection of occult metastasis and could have also influenced treatment algorithms. Because neither IHC status of the SLNs nor adjuvant therapy administration was significantly associated with either DFS or OS, the differences in treatment observed in this study are not clinically significant. The overall lower use of adjuvant systemic therapy in this study is likely accounted for in part by differences in patient population and treating physicians as well as difficulties in data collection of patients treated elsewhere.

One other study that is similar to the current study is a small, retrospective study by Wernicke et al[19] of 136 patients with SLNs that were all negative on HE staining alone, treated with BCS with a 9.9-year median follow-up time. The reported 10-year progression-free survival was 88.2%, with a 0% axillary recurrence rate, a 5.1% IBTR rate, and an 8.1% rate of distant disease. The overall disease recurrence rate was 13.2% for their patients with early-stage disease who had tumor-free SLNs.

Factors that were prognostic of DFS in the current study, including higher tumor grade and larger tumor, were entirely expected. Numerous studies have shown that tumor grade is a significant prognostic factor for DFS in patients with node-negative breast cancer.[11,18] Likewise, not surprisingly, worse OS was predicted by older age and larger tumor. More interestingly, this study found a correlation between patients who undergo BCS and improved survival compared with those undergoing mastectomy. This is not likely a causative relationship, however, and further data would be needed to account for this difference.

There are important limitations to the current study. The retrospective design introduces selection bias. The study design does not allow capture and analysis of all patients with IHC-positive lymph nodes, as some proportion would have gone on to have ALNDs and would have been excluded. Further, there is no control over possible pathology re-review of HE-negative SLNs that were later deemed to be HE positive after IHC evaluation. This number is likely to be very small; however, this study is not designed to address this possibility.

In addition, all retrospective studies have flaws in data acquisition. This is particularly true for patients undergoing adjuvant systemic therapy at distant sites where data recording may not have been adequate, offering a possible explanation for observed lower rates of adjuvant systemic therapy administration in this study. On the other hand, the retrospective design is also an advantage of the current study. Not all patients with breast cancer will accrue to randomized trials, leaving a poten-

tial selection bias as well for larger prospective clinical trials. The fact that the 5-year survival rates in this study are similar to the 5-year rates in both B-32 and Z0010, even though adjuvant systemic therapy may have been less frequently administered or recorded, provides validity to the survival results of this study. Nonetheless, the study does not suggest equivalence of lower rates of adjuvant systemic therapy administration to standard treatment recommendations.

In summary, more than 90% of patients in this study of patients with HE-negative SLNs did not develop disease recurrence at a median follow-up of 103.1 months. Only 2 developed isolated axillary recurrences. Of the 30 patients who developed distant disease, half, or only 1.8% of the study population, died with their breast cancer. These long-term data are consistent with those of prior published studies and support that patients with HE-negative SLNs should be managed without ALND and without additional IHC stains of their lymph nodes.

This study reports the long-term follow-up of a large cohort of patients with breast cancer and HE-negative SLNs, showing a remarkably low 0.2% axillary recurrence and high DFS. The accuracy, efficacy, and safety of SLNB alone in early, node-negative breast cancer are clear. Neither the addition of ALND nor IHC analysis of SLNs will contribute to a significant survival benefit as survival at 10 years is already high.

Accepted for Publication: April 20, 2012.
Published Online: July 16, 2012. doi:10.1001/archsurg.2012.1563
Correspondence: Armando E. Giuliano, MD, Departments of Surgery and Surgical Oncology, Samuel Oschin Comprehensive Cancer Institute, 310 N San Vicente Blvd, Los Angeles, CA 90048 (armando.giuliano@cshs.org).
Author Contributions: *Study concept and design:* Kapoor and Giuliano. *Acquisition of data:* Kapoor, Lin, and Giuliano. *Analysis and interpretation of data:* Kapoor, Sim, and Giuliano. *Drafting of the manuscript:* Kapoor and Giuliano. *Critical revision of the manuscript for important intellectual content:* Sim, Lin, and Giuliano. *Statistical analysis:* Sim. *Obtained funding:* Giuliano. *Administrative, technical, and material support:* Giuliano. *Study supervision:* Lin and Giuliano.
Financial Disclosure: None reported.
Funding/Support: This work was supported by the Associates for Breast and Prostate Cancer Studies, Santa Monica, California; QVC and the Fashion Footwear Association of New York Charitable Foundation, New York, New York; and the Margie and Robert E. Petersen Foundation, Los Angeles, California.
Previous Presentation: This paper was presented at the 83rd Annual Meeting of the Pacific Coast Surgical Association; February 18, 2012; Napa Valley, California; and is published after peer review and revision.

REFERENCES

1. Fisher B, Bauer M, Wickerham DL, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer: an NSABP update. *Cancer*. 1983;52(9):1551-1557.
2. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-933.
3. Veronesi U, Viale G, Paganelli G, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. *Ann Surg*. 2010;251(4):595-600.
4. Fougo JL, Dinis-Ribeiro M, Araújo C, et al. Impact of lymphadenectomy on axillary recurrence and morbidity of the upper limb in breast cancer patients with negative sentinel node: a prospective randomised study [in Spanish]. *Cir Esp*. 2011;89(5):307-316.
5. Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life: results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat*. 2006;95(3):279-293.
6. Lucci A, McCall LM, Beitsch PD, et al; American College of Surgeons Oncology Group. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol*. 2007;25(24):3657-3663.
7. Ashikaga T, Krag DN, Land SR, et al; National Surgical Adjuvant Breast, Bowel Project. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection vs axillary dissection. *J Surg Oncol*. 2010;102(2):111-118.
8. Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg*. 1995;222(3):394-401.
9. Cote RJ, Peterson HF, Chaiwun B, et al; International Breast Cancer Study Group. Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. *Lancet*. 1999;354(9182):896-900.
10. van der Heiden-van der Loo M, Bezemer PD, Hennipman A, et al. Introduction of sentinel node biopsy and stage migration of breast cancer. *Eur J Surg Oncol*. 2006;32(7):710-714.
11. Hansen NM, Grube B, Ye X, et al. Impact of micrometastases in the sentinel node of patients with invasive breast cancer. *J Clin Oncol*. 2009;27(28):4679-4684.
12. Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA*. 2011;306(4):385-393.
13. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med*. 2011;364(5):412-421.
14. Takeshita T, Tsuda H, Moriya T, et al. Clinical implications of occult metastases and isolated tumor cells in sentinel and non-sentinel lymph nodes in early breast cancer patients: serial step section analysis with long-term follow-up. *Ann Surg Oncol*. 2012;19(4):1160-1166.
15. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg*. 1994;220(3):391-401.
16. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg*. 1997;226(3):271-278.
17. Edge SE. Breast cancer. In: Edge SE, Byrd DR, Compton C, et al, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
18. Darby S, McGale P, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707-1716.
19. Wernicke AG, Goodman RL, Turner BC, et al. A 10-year follow-up of treatment outcomes in patients with early stage breast cancer and clinically negative axillary nodes treated with tangential breast irradiation following sentinel lymph node dissection or axillary clearance. *Breast Cancer Res Treat*. 2011;125(3):893-902.