Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis
A Randomized Clinical Trial

Armando E. Giuliano, MD

Kelly K. Hunt, MD

Karla V. Ballman, PhD

Peter D. Beitsch, MD

Pat W. Whitworth, MD

Peter W. Blumencranz, MD

A. Marilyn Leitch, MD

Sukamal Saha, MD

Linda M. McCall, MS

Monica Morrow, MD

AXILLARY LYMPH NODE DISSECtion (ALND) has been part of breast cancer surgery since the description of the radical mastectomy.[1] ALND reliably identifies nodal metastases and maintains regional control,[2,3] but the contribution of local therapy to breast cancer survival is controversial.[4,5] The Early Breast Cancer Trialists' Collaborative Group synthesized findings from 78 randomized controlled trials, concluding that local control of breast cancer was associated with improved disease-specific survival.[6]

ALND, as a means for achieving local disease control, carries an indisputable and often unacceptable risk of complications such as seroma, infection, and lymphedema.[7-9] Sentinel lymph node dissection (SLND) was therefore developed to accurately stage tumordraining axillary nodes with less morbidity than ALND.[10] SLND alone is the accepted management for patients whose

Context Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival.

Objective To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer.

Design, Setting, and Patients The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Interventions All patients underwent lumpectomy and tangential whole-breast irradiation. Those with SLN metastases identified by SLND were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of 10 or more nodes. Systemic therapy was at the discretion of the treating physician.

Main Outcome Measures Overall survival was the primary end point, with a noninferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is noninferior to ALND. Disease-free survival was a secondary end point.

Results Clinical and tumor characteristics were similar between 445 patients randomized to ALND and 446 randomized to SLND alone. However, the median number of nodes removed was 17 with ALND and 2 with SLND alone. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%-94.5%) with ALND and 92.5% (95% CI, 90.0%-95.1%) with SLND alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%-86.3%) with ALND and 83.9% (95% CI, 80.2%-87.9%) with SLND alone. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56-1.11) without adjustment and 0.87 (90% CI, 0.62-1.23) after adjusting for age and adjuvant therapy.

Conclusion Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

Trial Registration clinicaltrials.gov Identifier: NCT00003855

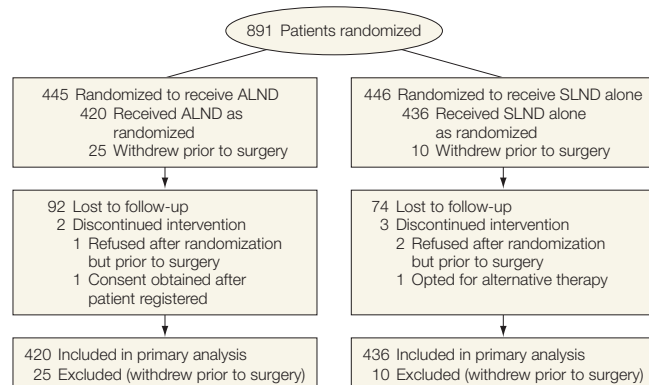*JAMA. 2011;305(6):569-575*   www.jama.com

Author Affiliations: John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, California (Dr Giuliano); M. D. Anderson Cancer Center, Houston, Texas (Dr Hunt); Mayo Clinic Rochester, Rochester, Minnesota (Dr Ballman); Dallas Surgical Group, Dallas, Texas (Dr Beitsch); Nashville Breast Center, Nashville, Tennessee (Dr Whitworth); Morton Plant Hospital, Clearwater, Florida (Dr Blumencranz); University of Texas Southwestern Medical Center, Dallas (Dr Leitch); McLaren Regional Medical Center, Michigan State University, Flint (Dr Saha); American College of Surgeons Oncology Group, Durham, North Carolina (Ms McCall); and Memorial Sloan-Kettering Cancer Center, New York, New York (Dr Morrow).
Corresponding Author: Armando E. Giuliano, MD, John Wayne Cancer Institute at Saint John's Health Center, 2200 Santa Monica Blvd, Santa Monica, CA 90404 (giulianoa@jwci.org).

Figure 1. Study Flow

ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

sentinel lymph nodes (SLNs) are histologically free of tumor, while ALND remains the standard of care for patients whose SLNs contain metastases.[11]

Cancer biology is much better understood now than it was when ALND was introduced. Biological factors may affect the predilection of some malignant cells to selectively invade lymph nodes rather than visceral organs, just as certain tumor types metastasize to certain organs and not others.[12] Recognition of the complexity of tumor biology has changed cancer treatment, with more liberal use of systemic therapy to treat occult cancer cells wherever they may be in the body. Consequently, the decision to administer systemic therapy is influenced by a variety of patient- and tumor-related factors, with lymph node tumor status influencing[13,14] but not necessarily dictating the use of chemotherapy.[15-18] Other factors, such as early cancer detection by screening mammography, have led to earlier intervention in breast cancer, reducing the incidence of nodal metastases and even the number of tumor-involved lymph nodes.[19]

These evolving concepts have called into question the need for ALND.[20,21] A variety of algorithms have been developed to help clinicians decide which patients would benefit from ALND.[22-24] Review of Surveillance, Epidemiology, and End Results data has shown that the use of ALND for SLN metastases has decreased in recent years.[25] No study has conclusively demonstrated a survival benefit or detriment for omitting ALND when metastatic breast cancer is identified by SLND. In the late 1990s, the American College of Surgeons Oncology Group designed and began the multicenter Z0011 trial. The primary aim of this study was to determine the effects of ALND on overall survival in patients with SLN metastases treated in the contemporary era with lumpectomy, adjuvant systemic therapy, and tangential-field radiation therapy.

METHODS
Patient Characteristics
This multicenter, randomized phase 3 trial was registered with the National Cancer Institute and approved by the institutional review boards of participating centers. All patients provided written informed consent. Adult women with histologically confirmed invasive breast carcinoma clinically 5 cm or less, no palpable adenopathy, and an SLN containing metastatic breast cancer documented by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section were eligible for participation. Patients with metastases identified initially or solely with immunohistochemical staining were ineligible. Treatment with lumpectomy to negative margins (no tumor at ink) was required. Women were ineligible if they had 3 or more positive SLNs, matted nodes, or gross extranodal disease, or if they had received neoadjuvant hormonal therapy or chemotherapy.

Study Design and Treatment
Before randomization, all women underwent SLND and were stratified according to age ($\leq$50 and $>$50 years), estrogen-receptor status, and tumor size ($\leq$1 cm, $>$1 cm and $\leq$2 cm, or $>$2 cm). Eligible women were randomly assigned to ALND or no further axillary-specific intervention—specifically, no third-field nodal irradiation. ALND was defined as an anatomical level I and II dissection including at least 10 nodes. All women were to receive whole-breast opposing tangential-field radiation therapy. The use of adjuvant systemic therapy was determined by the treating physician and was not specified in the protocol.

Patients most commonly entered the study post-SLND following identification of metastases on final pathology report. However, of the 891 registered patients, 287 were registered pre-SLND and assigned to treatment after intraoperative documentation of SLN metastases. Patients in this group subsequently found to have 3 or more tumor-involved lymph nodes were included in the analysis. Patients were assessed for disease recurrence according to standard clinical practice. History and physical examination were performed every 6 months for the first 36 months and yearly thereafter. Annual mammography was required; other testing was based on symptoms and investigator preference.

Study End Points
The primary end point was overall survival, defined as the time from randomization until death from any cause. A short-term primary end point was occurrence of surgical morbidities. The study plan was to report surgical morbidities following the completion of accrual and prior to overall survival reporting after receiving permission from the data and safety monitoring committee. These morbidities have been reported.[10]

A secondary end point was disease-free survival, defined as the time from

randomization to death or first documented recurrence of breast cancer. Breast cancer recurrence was categorized as locoregional disease (tumor in the breast or ipsilateral supraclavicular, subclavicular, internal mammary, or axillary nodes) or distant metastases. Disease-free survival and its components (locoregional disease and distant metastases) are reported instead of the protocol-specified secondary end point (eg, distant disease–free survival) to facilitate comparison with other studies.

Statistical Analysis

The primary end point was overall survival as a measure of noninferiority of no further axillary specified interventions (SLND-alone group) compared with the ALND group. Based on the literature at the time of study design, we hypothesized that overall survival was 80% at 5 years for optimally treated women with positive nodes.[26-28] Clinical noninferiority was defined as the SLND-alone group having a 5-year survival of not less than 75% of that observed in the ALND group. Noninferiority of the SLND-alone treatment was also considered if the hazard ratio (HR) for mortality was less than 1.3 when compared with ALND. An estimated 500 deaths were needed for the study to have 90% power to confirm noninferiority of SLND alone compared with ALND, with the use of a 2-sided 90% confidence interval (CI) for the HR from a Cox regression model.[29] Specifically, if the 90% CI for the HR was below 1.3, this would indicate that patients undergoing SLND alone do not have an unacceptably worse overall survival than patients undergoing SLND plus ALND.

The use of a 2-sided 90% CI corresponds to a 1-sided significance level of .05.[30] The enrollment of 1900 patients in 4 years with a minimum follow-up period of 5 years was initially planned. Four formal interim analyses and 1 final analysis were planned for overall survival, and the O'Brien-Flemming α-spending strategy was used to generate stopping boundaries for each planned analysis. The overall study significance was maintained at .05. However, none of the planned interim analyses were performed before the study was closed based on the recommendation of the data and safety monitoring committee. Because of this, a single terminal hypothesis test with an α of .05 is applied to the data, which makes it consistent with the planned overall significance level of .05 in the original study plan.

Ineligible patients were retained in all analyses (ie, both the intent-to-treat analyses and the treatment-received analyses). Kaplan-Meier survival curves for overall survival were compared by log-rank test. The unadjusted HR (and 90% CI) was calculated using a Cox regression analysis, and noninferiority P values are reported. As a secondary analysis, known prognostic factors including adjuvant treatment were included in the Cox regression model to generate an adjusted HR for overall survival (with a 90% CI and noninferiority P values). Disease-free survival was analyzed using Kaplan-Meier curves and univariable and multivariable Cox regression analyses with 95% CIs. The fact that there were only 94 deaths limited the number of variables that could be used in a multivariable model without affecting model stability. We created a base model that included the treatment group (SLND alone vs ALND), age (≤50 vs >50 years), and whether the patient received adjuvant therapy (yes vs no) and added prognostic variables to this model individually. Only variables obtained on 90% or more of the patients were included in the multivariable analysis. Locoregional recurrence rates were compared with the Fisher exact test. Each analysis, other than analysis for the primary end point of overall survival, was performed with 2-sided P values, 5% significance, and a 95% CI; all analyses were performed using SAS release 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS
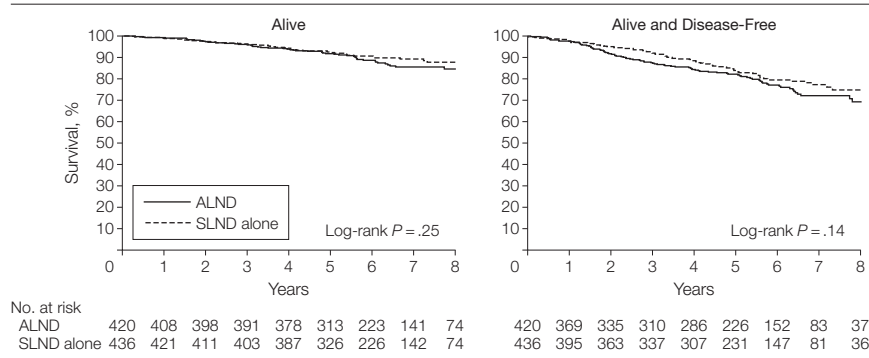
Patient Characteristics

The first patient was enrolled in May 1999, and accrual closed in December 2004 based on a recommendation of the independent data and safety monitoring committee because of concerns regarding the extremely low mortality rate. Even if the trial had accrued the targeted 1900 patients, it would have taken more than 20 years of follow-up to observe 500 deaths at the realized event rate. At the time of the decision to terminate the study there had been no formal analysis comparing the survival experience between the 2 groups; the decision was based solely on the ob-

Table 1. Baseline Patient and Tumor Characteristics by Study Group

Characteristic	No. (%) ALND (n = 420)	No. (%) SLND Alone (n = 436)
Age, median (range), y	56 (24-92)	54 (25-90)
Missing	7	10
Clinical T stage		
T1	284 (67.9)	303 (70.6)
T2	134 (32.1)	126 (29.4)
Missing	2	7
Tumor size, median (range), cm	1.7 (0.4-7.0)	1.6 (0.0-5.0)
Missing	6	14
Receptor status		
ER+/PR+	256 (66.8)	270 (68.9)
ER+/PR−	61 (15.9)	54 (13.8)
ER−/PR+	3 (0.8)	4 (1.0)
ER−/PR−	63 (16.5)	64 (16.3)
Missing	37	44
LVI		
Yes	129 (40.6)	113 (35.2)
No	189 (59.4)	208 (64.8)
Missing	102	115
Modified Bloom-Richardson score		
1	71 (22.0)	81 (25.6)
2	158 (48.9)	148 (46.8)
3	94 (29.1)	87 (27.5)
Missing	97	120
Tumor type		
Infiltrating ductal	344 (82.7)	356 (84.0)
Infiltrating lobular	27 (6.5)	36 (8.5)
Other	45 (10.8)	32 (7.5)
Missing	4	12
Lymph node metastases		
0	4 (1.2)	29 (7.0)
1	199 (58.0)	295 (71.1)
2	68 (19.8)	76 (18.3)
3	25 (7.3)	11 (2.7)
≥4	47 (13.7)	4 (1.0)
Missing	77	21

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; LVI, lymphovascular invasion; PR, progesterone receptor; SLND, sentinel lymph node dissection.

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group

ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

and 277 of 309 (89.6%) in the SLND-alone group.

Overall Survival

At a median follow-up of 6.3 years (IQR, 5.2-7.7), there were 94 deaths (SLND-alone group, 42; ALND group, 52). The use of SLND alone compared with ALND did not appear to result in statistically inferior survival (**FIGURE 2**) (P=.008 for noninferiority). The unadjusted HR comparing overall survival between the SLND-alone group and the ALND group was 0.79 (90% CI, 0.56-1.10), which did not cross the specified boundary of 1.3 (**FIGURE 3**). The 5-year overall survival rates were 92.5% (95% CI, 90.0%-95.1%) in the SLND-alone group and 91.8% (95% CI, 89.1%-94.5%) in the ALND group. This was substantially greater than the 80% anticipated at protocol design. The HR for overall survival adjusting for adjuvant therapy (chemotherapy, endocrine therapy, and/or radiation therapy) and age for the SLND-alone group compared with the ALND group was 0.87 (90% CI, 0.62-1.23). The adjusted HRs comparing the SLND-alone group with the ALND group in the other multivariable models ranged from 0.86 to 0.92 (**TABLE 2**), all similar to the unadjusted rate of 0.79. An exploratory analysis revealed that treatment with ALND vs SLND alone produced no statistically significant difference in outcome among patients grouped by receptor status of the primary tumor (ER+/PR+ or ER–/PR–).

Disease-Free Survival

Disease-free survival (Figure 2) did not differ significantly between treatment groups. The 5-year disease-free survival was 83.9% (95% CI, 80.2%-87.9%) for the SLND-alone group and 82.2% (95% CI, 78.3%-86.3%) for the ALND group (P=.14). The unadjusted HR comparing the SLND-alone group with the ALND group was 0.82 (95% CI, 0.58-1.17), and the HR adjusted for adjuvant treatment and age was 0.88 (95% CI, 0.62-1.25) (**TABLE 3**). The adjusted HRs comparing the SLND-alone group with the ALND group in the other multivari-

served mortality rate for pooled data from the 2 groups. The date of last follow-up for this analysis was March 4, 2010.

Patients were enrolled from 115 institutions, which included affiliates of the Cancer Trials Support Unit and the North Central Cancer Treatment Group. Of 891 patients, 445 were randomly assigned to the ALND group and 446 to the SLND-alone group (**FIGURE 1**). Thirty-five patients were excluded after withdrawing consent prior to surgery. The 103 ineligible patients were included in the analyses reported here. Because this was a noninferiority trial, a more conservative analysis was performed on the treatment-received sample (n=813 patients); 32 patients in the ALND group did not have ALND, and 11 patients in the SLND-alone group had ALND. No qualitative differences were observed between treatment-received sample and intent-to-treat sample analyses, so only intent-to-treat results are reported. Disease characteristics at baseline were well balanced between the 2 groups (**TABLE 1**).

Treatment Results

There was an expected difference between ALND and SLND-alone treatment groups in total number of removed lymph nodes and total number of tumor-involved nodes; the median total number of nodes removed was 17 (interquartile range [IQR], 13-22) in the ALND group and 2 (IQR, 1-4) in the SLND-alone group.[31] The median total

number of nodes with histologically demonstrated tumor involvement (including SLNs) in the ALND group and SLND-alone group was equal (1 [IQR, 1-2] for both groups). Hematoxylin-eosin–stained tumor deposits no larger than 2 mm were defined as micrometastases and were identified in SLNs of 137 of 365 patients (37.5%) in the ALND group compared with 164 of 366 (44.8%) in the SLND-alone group (P=.05). In the ALND group, 97 of 355 patients (27.3%) had additional metastasis in lymph nodes removed by ALND, including 10% of patients with SLN micrometastasis who had macroscopically involved non-SLNs removed. Total nodal involvement is summarized in Table 1; 21.0% of patients undergoing ALND had 3 or more involved nodes compared with 3.7% undergoing SLND alone. Four or more involved nodes were seen in 13.7% of patients receiving ALND and 1.0% of those receiving SLND alone.

Adjuvant systemic therapy was delivered to 403 women (96.0%) in the ALND group and 423 women (97.0%) in the SLND-alone group.[31] No differences in the proportion of women receiving endocrine therapy, chemotherapy, or both were observed. The type of chemotherapy administered was similar in the 2 groups; anthracycline- and taxane-based combination regimens were the most common. The majority of the women (n=605) received whole-breast radiation therapy: 263 of 296 (88.9%) in the ALND group

able models ranged from 0.84 to 0.89 (Table 3), all similar to the unadjusted rate of 0.82. Locoregional recurrence and its correlates have been previously reported.[31] The 5-year rates of local recurrence were 1.6% (95% CI, 0.7%-3.3%) in the SLND-alone group and 3.1% (95% CI, 1.7%-5.2%) in the ALND group (*P*=.11). Locoregional recurrence–free survival at 5 years was 96.7% (95% CI, 94.7%-98.6%) in the SLND-alone group and 95.7% (95% CI, 93.6%-97.9%) in the ALND group (*P*=.28).

Surgical Morbidities

Paresthesias, shoulder pain, weakness, lymphedema, and axillary web syndrome are recognized morbidities of ALND.[7-9] As previously reported,[10] the rate of wound infections, axillary seromas, and paresthesias among patients in the Z0011 trial was higher for the ALND group than for the SLND-alone group (70% vs 25%, *P*<.001). Lymphedema in the ALND group was significantly more common by subjective report (*P*<.001) and also tended to be higher by objective assessment of arm circumference. These findings are in accordance with other randomized comparisons of SLND with vs without ALND.[32,33]
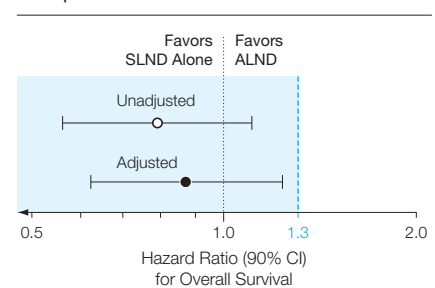
COMMENT

In the American College of Surgeons Oncology Group Z0011 randomized trial, ALND did not significantly affect overall or disease-free survival of patients with clinical T1-T2 breast cancer and a positive SLN who were treated with lumpectomy, adjuvant systemic therapy, and tangential-field whole-breast radiation therapy. These survival findings are consistent with those of the National Surgical Adjuvant Breast and Bowel Project B04 trial, in which women with clinically negative nodes were randomized to treatment by radical mastectomy, total mastectomy plus nodal irradiation, or total mastectomy with delayed ALND if nodal recurrence was observed.[4] Initially and at each interim analysis for up to 25 years of follow-up, no statistically significant survival differences were observed between any of the groups. For patients treated in the modern era, the relevance of the B04 study, which included patients with larger tumors undergoing mastectomy without adjuvant systemic therapy, is uncertain, because an axillary recurrence after SLND in patients with a lower risk of death from distant disease might negatively affect

survival. The findings from Z0011 document the high rate of locoregional control achieved with modern multimodality therapy, even without ALND.

In contrast to B04, in which about 40% of patients in the radical mastectomy group were node-positive and the same number in the total mastectomy group were assumed to be node-positive and 5-year overall survival was only about 60%, 100% of patients in Z0011 had nodal involvement; yet the 5-year over-

Figure 3. Hazard Ratios Comparing Overall Survival Between the ALND and SLND-Alone Groups

Blue dashed line at hazard ratio=1.3 indicates noninferiority margin; blue-tinted region to the left of hazard ratio=1.3 indicates values for which SLND alone would be considered noninferior to SLND plus ALND. ALND indicates axillary lymph node dissection; CI, confidence interval; SLND, sentinel lymph node dissection.

Table 2. Adjusted Hazard Ratios for Overall Survival Comparing SLND-Alone vs ALND Groups

Model Variables	No.		Adjusted HR (90% CI)	Noninferiority P Value
	Patients	Events		
Treatment group (SLND alone vs ALND), age (≤50 vs >50 y), adjuvantly treated (yes vs no)	839	92	0.87 (0.62-1.23)	.03
Variables in row 1 + primary tumor size (per 1 cm, continuous)	818	92	0.89 (0.62-1.25)	.03
Variables in row 1 + estrogen receptor status (negative vs positive)	778	87	0.92 (0.64-1.30)	.05
Variables in row 1 + modified Bloom-Richardson score (1 vs 2 vs 3)	839	92	0.86 (0.61-1.21)	.02
Variables in row 1 + tumor type (ductal vs lobular vs other)	839	92	0.88 (0.63-1.25)	.03

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLND, sentinel lymph node dissection.

Table 3. Adjusted Hazard Ratios for Disease-Free Survival Comparing SLND-Alone vs ALND Groups

Model Variables	No.		Adjusted HR (95% CI)	P Value
	Patients	Events		
Treatment group (SLND alone vs ALND), age (≤50 vs >50 y), adjuvantly treated (yes vs no)	839	127	0.88 (0.62-1.25)	.47
Variables in row 1 + primary tumor size (per 1 cm, continuous)	818	125	0.86 (0.60-1.22)	.40
Variables in row 1 + estrogen receptor status (negative vs positive)	778	117	0.84 (0.58-1.20)	.33
Variables in row 1 + modified Bloom-Richardson score (1 vs 2 vs 3)	839	127	0.87 (0.61-1.23)	.43
Variables in row 1 + tumor type (ductal vs lobular vs other)	839	127	0.89 (0.62-1.27)	.52

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLND, sentinel lymph node dissection.

all survival was more than 90%. Furthermore, a 19% rate of axillary first failure was observed in B04,[4] whereas the axillary nodal recurrence rate was only 0.9% in the SLND-alone group in Z0011.[31] The excellent local and distant outcomes in this study highlight the effects of multiple changes in breast cancer management during the interval between the 2 studies. These changes, which include improved imaging, more detailed pathological evaluation, improved planning of surgical and radiation approaches, and more effective systemic therapy, emphasize the need for ongoing reevaluation of "standard" local therapy.

The well-documented morbidity from ALND has led other investigators to explore alternative methods of axillary treatment in patients with clinically negative nodes, including radiation, systemic therapy, and axillary observation. These have consistently demonstrated low axillary failure rates, with no significant differences in survival.[34,35] The International Breast Cancer Study Group trial of ALND vs observation is noteworthy because more than half of the patients did not receive breast or axillary radiotherapy. In women 60 years and older receiving adjuvant tamoxifen but no axillary treatment, the rate of axillary recurrence was only 3%, and overall survival was 73% at a median follow-up of 6.6 years.[36]

The low rates of locoregional recurrence at 5 years and the nearly identical overall and disease-free survival between treatment groups in Z0011 would suggest that differences in survival between study groups are unlikely to emerge with longer follow-up, because ALND would only affect survival by virtue of improved locoregional control. In the Early Breast Cancer Trialists' Collaborative Group overview, statistically significant survival differences between treatments at 15 years were seen only when differences in locoregional recurrence between treatments were greater than 10% at 5 years.[6] Axillary recurrence is usually an early event, occurring at a median of 14.8 months in B04; in that trial, only 7 of 68 axillary recurrences occurred

more than 5 years after study entry.[4] Greco et al[37] reported that median time to axillary recurrence was 30.6 months for 401 patients who underwent breast-conserving procedures and radiation therapy with no axillary surgery. Recent reports of long-term follow-up in randomized trials confirm these findings.[38,39] Because the total locoregional recurrence rate in the Z0011 SLND-alone group at 5 years is only 2.5% compared with 3.6% in the ALND group, it is unlikely that further follow-up would result in enough additional recurrences to generate a clinically meaningful survival difference between groups. The absolute difference in 5-year overall survival between the treatment groups in Z0011 is 0.7%, numerically favoring the SLND-alone group. The HR for overall survival comparing the SLND-alone group with the ALND group was 0.79 (90% CI, 0.56-1.10). The worst HR (1.10) is less than 1.3, which was hypothesized as the inferiority margin threshold. In essence, this means that the 5-year overall survival for the SLND-alone group might be as low as 90.3% if the true 5-year overall survival for the ALND group was 91.8% and the HR as high as 1.10. Most importantly, there is no suggestion that rates of locoregional recurrence, the mechanism by which variations in local therapy result in survival differences, differ between groups to the extent needed to produce survival differences or are likely to do so in the future. Taken together, this suggests that contemporary women may sustain the morbidity of ALND without any meaningful improvement in survival rates. Limitations of the study, such as failure to achieve target accrual and possible randomization imbalance favoring the SLND-alone group, must be considered. However, even in high-risk women (ER–/PR–) in Z0011, preliminary analysis suggests no effect of elimination of ALND on survival.

Despite limitations of the Z0011 trial, its findings could have important implications for clinical practice. Examination of the regional nodes with SLND can identify hematoxylin-eosin–detected me-

tastases that would indicate a higher risk for systemic disease and the need for systemic therapy to reduce that risk. Results from Z0011 indicate that women with a positive SLN and clinical T1-T2 tumors undergoing lumpectomy with radiation therapy followed by systemic therapy do not benefit from the addition of ALND in terms of local control, disease-free survival, or overall survival. The only additional information gained from ALND is the number of nodes containing metastases. This prognostic information is unlikely to change systemic therapy decisions and is obtained at the cost of a significant increase in morbidity.[10] The only rationale for ALND in these patients would be if the finding of additional nodal metastases would result in changes in systemic therapy. Because current guidelines do not support differences in adjuvant systemic therapy based on the number of positive lymph nodes, except in some uncommon select subgroups,[40] ALND does not appear to be warranted in this patient population.

The Z0011 trial did not include patients undergoing mastectomy, those undergoing lumpectomy without radiotherapy, those treated with partial-breast irradiation, those receiving neoadjuvant therapy, and those receiving whole-breast irradiation in the prone position, in which the low axilla is not treated. In those patients, ALND remains standard practice when SLND identifies a positive SLN. However, ALND may no longer be justified for women who have clinical T1-T2 breast cancer and hematoxylin-eosin–detected metastasis in the SLN and who are treated with breast-conserving surgery, whole-breast irradiation, and adjuvant systemic therapy. Implementation of this practice change would improve clinical outcomes in thousands of women each year by reducing the complications associated with ALND and improving quality of life with no diminution in survival.

REFERENCES

1. Halsted WS. The results of radical operations for the cure of carcinoma of the breast. *Ann Surg.* 1907; 46(1):1-19.

2. Fisher B, Wolmark N, Bauer M, Redmond C, Gebhardt M. The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. *Surg Gynecol Obstet.* 1981;152(6):765-772.

3. Graversen HP, Blichert-Toft M, Andersen JA, Zedeler K. Breast cancer: risk of axillary recurrence in node-negative patients following partial dissection of the axilla. *Eur J Surg Oncol.* 1988;14(5):407-412.

4. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med.* 2002;347(8):567-575.

5. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival—a Bayesian meta-analysis. *Ann Surg Oncol.* 1999;6(1):109-116.

6. Clarke M, Collins R, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366(9503):2087-2106.

7. Yeoh EK, Denham JW, Davies SA, Spittle MF. Primary breast cancer: complications of axillary management. *Acta Radiol Oncol.* 1986;25(2):105-108.

8. Lotze MT, Duncan MA, Gerber LH, Woltering EA, Rosenberg SA. Early versus delayed shoulder motion following axillary dissection: a randomized prospective study. *Ann Surg.* 1981;193(3):288-295.

9. Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. *Br J Cancer.* 1992;66(1):136-138.

10. 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.

11. Lyman GH, Giuliano AE, Somerfield MR, et al; American Society of Clinical Oncology. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol.* 2005;23(30):7703-7720.

12. Fidler IJ. The pathogenesis of cancer metastasis: the "seed and soil" hypothesis revisited. *Nat Rev Cancer.* 2003;3(6):453-458.

13. Abrams JS. Adjuvant therapy for breast cancer—results from the USA consensus conference. *Breast Cancer.* 2001;8(4):298-304.

14. Goldhirsch A, Glick JH, Gelber RD, Senn HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. *J Natl Cancer Inst.* 1998;90(21):1601-1608.

15. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A.* 2001;98(19):10869-10874.

16. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med.* 2002;347(25): 1999-2009.

17. Albain KS, Barlow WE, Shak S, et al; Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol.* 2010;11(1):55-65.

18. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* 2006;24(23):3726-3734.

19. Swedish Organised Service Screening Evaluation Group. Effect of mammographic service screening on stage at presentation of breast cancers in Sweden. *Cancer.* 2007;109(11):2205-2212.

20. Fisher B, Montague E, Redmond C, et al. Comparison of radical mastectomy with alternative treatments for primary breast cancer: a first report of results from a prospective randomized clinical trial. *Cancer.* 1977;39(6)(suppl):2827-2839.

21. Rutgers EJ. Sentinel node biopsy: interpretation and management of patients with immunohistochemistry-positive sentinel nodes and those with micrometastases. *J Clin Oncol.* 2008;26(5):698-702.

22. van la Parra RF, Ernst MF, Bevilacqua JL, et al. Validation of a nomogram to predict the risk of nonsentinel lymph node metastases in breast cancer patients with a positive sentinel node biopsy: validation of the MSKCC breast nomogram. *Ann Surg Oncol.* 2009;16(5):1128-1135.

23. Amanti C, Lombardi A, Maggi S, et al. Is complete axillary dissection necessary for all patients with positive findings on sentinel lymph node biopsy? validation of a breast cancer nomogram for predicting the likelihood of a non-sentinel lymph node. *Tumori.* 2009; 95(2):153-155.

24. Coutant C, Olivier C, Lambaudie E, et al. Comparison of models to predict nonsentinel lymph node status in breast cancer patients with metastatic sentinel lymph nodes: a prospective multicenter study. *J Clin Oncol.* 2009;27(17):2800-2808.

25. Rescigno J, Zampell JC, Axelrod D. Patterns of ax-

illary surgical care for breast cancer in the era of sentinel lymph node biopsy. *Ann Surg Oncol.* 2009; 16(3):687-696.

26. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med.* 1989;320(13):822-828.

27. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet.* 1992;339 (8785):71-85.

28. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet.* 1992;339 (8784):1-15.

29. Rubinstein LV, Gail MH, Santner TJ. Planning the duration of a comparative clinical trial with loss to follow-up and a period of continued observation. *J Chronic Dis.* 1981;34(9-10):469-479.

30. Kaji AH, Lewis RJ. Are we looking for superiority, equivalence, or noninferiority? asking the right question and answering it correctly. *Ann Emerg Med.* 2010;55(5):408-411.

31. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg.* 2010;252(3):426-433.

32. Fleissig A, Fallowfield LJ, Langridge CI, et al. Postoperative 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.

33. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med.* 2003;349(6):546-553.

34. Veronesi U, Orecchia R, Zurrida S, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. *Ann Oncol.* 2005;16(3):383-388.

35. Martelli G, Boracchi P, De Palo M, et al. A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. *Ann Surg.* 2005; 242(1):1-9.

36. Rudenstam CM, Zahrieh D, Forbes JF, et al; International Breast Cancer Study Group. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol.* 2006;24(3):337-344.

37. Greco M, Agresti R, Cascinelli N, et al. Breast cancer patients treated without axillary surgery: clinical implications and biologic analysis. *Ann Surg.* 2000; 232(1):1-7.

38. Martelli G, Miceli R, Daidone MG, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up [published online ahead of print July 23, 2010]. *Ann Surg Oncol.* 2010. doi:10.1245/s10434-010-1217-7.

39. 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.

40. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ; Panel Members. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol.* 2009;20(8):1319-1329.