Published in final edited form as:

*JAMA*. 2011 February 09; 305(6): 569–575. doi:10.1001/jama.2011.90.

# Sentinel Lymph Node Dissection With and Without Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis: A Randomized Clinical Trial

**Armando E. Giuliano**[1], **Kelly K. Hunt**[2], **Karla. V. Ballman**[3], **Peter D. Beitsch**[4], **Pat W. Whitworth**[5], **Peter W. Blumencranz**[6], **A. Marilyn Leitch**[7], **Sukamal Saha**[8], **Linda M. McCall**[9], and **Monica Morrow**[10]

[1]John Wayne Cancer Institute, Santa Monica, CA

[2]MD Anderson Cancer Center, Houston, TX

[3]Mayo Clinic Rochester, Rochester, MN

[4]Dallas Surgical Group, Dallas, TX

[5]Nashville Breast Center, Nashville, TN

[6]Morton Plant Hospital, Clearwater, FL

[7]University of Texas Southwestern Medical Center, Dallas, TX

[8]McLaren Regional Medical Center, Michigan State University, Flint, MI

[9]American College of Surgeons Oncology Group, Durham, NC

[10]Memorial Sloan-Kettering Cancer Center, New York, NY

## Abstract

**Context—**Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer.

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

**Design and Setting—**The 115 sites participating in the American College of Surgeons Oncology Group Z0011 trial enrolled patients from May 1999 to December 2004. In this phase III noninferiority trial, patients with SLN metastasis were randomized to ALND or no further axillary treatment. Targeted enrollment was 1900 women, with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Corresponding author: Armando E. Giuliano, M.D., Chief of Science and Medicine, John Wayne Cancer Institute, 2200 Santa Monica Boulevard, Santa Monica, CA 90404, Telephone: 310-829-8089, giulianoa@jwci.org.

**Trial Registration:** Clinicaltrials.gov Identifier: NCT00003855

**Authors' Disclosure of Potential Conflict of Interest**

The authors indicate no potential conflicts of interest.

**Patients—**Women with clinical T1–T2 invasive breast cancer, no palpable adenopathy, and 1–2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin and eosin staining on permanent section.

**Interventions—**All patients underwent lumpectomy and tangential whole-breast irradiation. Those randomized to ALND underwent dissection of ≥10 nodes. Systemic therapy was at the discretion of the treating physician.

**Main Outcome Measures—**Overall survival (OS) was the primary endpoint, with a noninferiority margin of a one-sided hazard ratio of 1.3 or less favoring ALND. Disease-free survival (DFS) was a secondary endpoint.

**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 date 03/04/2010), 5-year OS was 91.8% (95% CI: 89.1 to 94.5) with ALND and 92.5% (95% CI: 90.0 to 95.1) with SLND alone; 5-year DFS was 82.2% (95% CI: 78.3 to 86.3) with ALND and 83.9% (95% CI: 80.2 to 87.9) with SLND alone. Hazard ratio for treatment-related OS was 0.79 (90% CI: 0.56 to 1.11) without adjustment and 0.87 (90% CI: 0.62 to 1.23) after adjusting for age and adjuvant therapy.

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

## Introduction

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 tumor-draining axillary nodes with less morbidity than ALND.[10] SLND alone is the accepted management for patients whose sentinel lymph nodes (SLN) 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. Biologic 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 less emphasis given to local disease control and the more liberal use of systemic chemotherapy in order 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 [17, 18] but not

necessarily dictating the use of chemotherapy.[13–16] Other factors, such as early cancer detection by screening mammography, has led to earlier intervention in breast cancer reducing the incidence of nodal metastases and even the number of tumor-involved nodes.[19]

The changes in the understanding and presentation of breast cancer has called into question the need for ALND.[20,24] A variety of algorithms have been developed in order to help clinicians decide which patients would benefit from ALND [21–23]. Review of SEER data has shown that the use of ALND for SLN metastases is decreasing.[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 (ACOSOG) designed and began the multicenter Z0011 trial. The primary aim of this study was to determine the impact of ALND on overall survival (OS) 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 III 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 females with histologically confirmed invasive breast carcinoma clinically ≤ 5 cm, no palpable adenopathy, and a SLN containing metastatic breast cancer documented by frozen section, touch preparation, or hematoxylin and eosin (H&E) 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 received neoadjuvant hormonal or chemotherapy.

### Study Design and Treatment

Before randomization, all women had SLND and were stratified according to age (≤50 years; >50 years), estrogen-receptor status, and tumor size (≤1 cm, >1 cm and ≤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 anatomic level I and II dissection including at least 10 nodes. All women were to receive whole breast opposing tangential field RT. 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. 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 tumor-involved lymph nodes were included in the analysis. Patients were assessed for disease recurrence according to standard clinical practice. History and physical exam 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 endpoint was overall survival (OS), defined as the time from randomization until death from any cause. A short-term primary endpoint was surgical morbidities. The study plan was to report surgical morbidities following the completion of accrual and prior to OS reporting after receiving permission from the Data Safety Monitoring Committee. These have been reported.[10] A secondary endpoint was disease-free survival (DFS), 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. DFS and its components (locoregional disease and distant metastases) are reported instead of the protocol-specified secondary endpoint (e.g., distant DFS) to facilitate comparison with other studies.

## Statistical Analysis

The primary endpoint was OS as a measure of non-inferiority of no further axillary-specified interventions (SLND-alone group) compared to the ALND group. Based on the literature at the time of study design, we hypothesized that OS was 80% at 5 years for optimally treated node-positive women.[26–28] The SLND-alone group would be considered clinically non-inferior to the ALND group if the 5-year survival rate was 75% or greater, a hazard ratio of 1.3 or less. An estimated 500 deaths were needed for the study to have a 90% power to confirm non-inferiority of SLND compared with ALND, with the use of a two-sided 90% confidence interval (CI) for the hazard ratio from a Cox regression model.[29] Specifically, if the 90% CI for the hazard ratio was below 1.3, this would indicate patients undergoing SLND alone do not have an unacceptably worse OS than patients undergoing SLND plus ALND. The use of a two-sided 90% confidence interval corresponds to a one-sided significance level of 0.05.[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 one final analysis were planned for OS, and O'Brien-Flemming alpha-spending strategy was used to generate stopping boundaries for each planned analysis. The overall study significance was maintained at 0.05. However, none of the planned interim analyses were performed before the study was closed based on the recommendation of the data monitoring committee. Because of this, a single terminal hypothesis test with an alpha of 0.05 is applied to the data, which makes it consistent with the planned overall significance level of 0.05 in the original study plan.

Ineligible patients were retained in all analyses: both the intent-to-treat analyses and the treatment-received analyses. Kaplan-Meier survival curves for OS were compared by log-rank test. The unadjusted hazard ratio (and 90% CI) was calculated using a Cox regression analysis and non-inferiority 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 hazard ratio for OS (with a 90% confidence interval and non-inferiority p-values). DFS was analyzed using Kaplan-Meier curves and univariable and

multivariable Cox regression analyses with 95% confidence intervals. The fact that there were only 94 deaths limited the number of variables that could be used in a multivariable model without impacting model stability. We created a base model that included the treatment arm (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 that were obtained on 90% or more of the patients were included in the multivariable analysis. Locoregional recurrence (LRR) rates were compared with Fisher's exact test. Each analysis, other than analysis for the primary endpoint of OS, was performed with a 2-sided, 5% significance and a 95% CI using SAS software, Release 9.1, SAS Institute.

## 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 monitoring committee due to 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 two groups; the decision was based solely on the observed mortality rate for pooled data from the two groups. The date of last follow-up for this analysis was 03/04/2010.

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. Since this was a noninferiority trial, a more conservative analysis was performed on the treatment-received sample (n=813 patients); 32 patients in ALND group did not have ALND, and 11 patients in SLND-alone group had ALND. No qualitative differences were observed between treatment-received sample and intent-to-treat sample (ITT) analyses, so only ITT 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 and number of involved lymph nodes removed; the median total number of nodes removed was 17 on the ALND group (interquartile range [IQR]: 13 to 22), and 2 on the SLND-alone group (IQR: 1 to 4). The median total number of histologically tumor-involved nodes (including SLNs) in the ALND group and SLND-alone group was equal: 1 (IQR: 1 to 2) and 1 (IQR: 1 to 2). H&E-stained tumor deposits no larger than 2 mm were defined as micrometastases and were identified in SLNs of 137 (37.5%) patients in the ALND group compared to 164 (44.8%) in the SLND-alone group (p=0.05). In the ALND group, 97 (27.3%) patients had additional metastasis in lymph nodes removed by ALND, including 10% of patients with SLN micrometastasis who had macroscopically involved non-SLN

removed. Total nodal involvement is summarized in Table 1; 21.0% of patients undergoing ALND had ≥3 involved nodes compared to 3.7% undergoing SLND alone. Four or more involved nodes were seen in 13.7% of ALND patients and 1.0% of SLND-alone patients.

Adjuvant systemic therapy was delivered to 403 women (96.0%) in the ALND group and 423 women (97.0%) in the SLND-alone group. No differences in the proportion of women receiving endocrine therapy and/or chemotherapy 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 received RT: 263 women (88.9%) in the ALND group and 277 women (89.6%) in the SLND-alone group.

## 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 the SLND-alone group (70% versus 25%, p≤0.001). Lymphedema in the ALND group was significantly more common by subjective report (p≤0.0001) and also tended to be higher by objective assessment of arm circumference. These findings are in accordance with other randomized comparisons of SLND with versus without ALND.[31, 32]

## Overall Survival

At a median follow-up of 6.3 years (IQR: 5.2 to 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 2a) (non-inferiority p=0.008). The unadjusted hazard ratio comparing OS between the SLND-alone group and the ALND group was 0.79 with a 90% CI of 0.56–1.10, which did not cross the specified boundary of 1.3. The 5-year OS rates were 92.5% (95% CI, 90.0–95.1%) and 91.8% (95% CI, 89.1–94.5%) in the SLND-alone and ALND groups, respectively. This was substantially greater than the 80% anticipated at protocol design. The hazard ratio for OS adjusting for adjuvant therapy (chemotherapy, endocrine therapy, and/or RT) and age for the SLND-alone group compared to the ALND group was 0.87 (90% CI, 0.62–1.23). The adjusted hazard ratios comparing SLND-alone group to 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 of the impact of ALND for patients with ER+/PR+ and ER−/PR− tumors was performed, revealing no statistically significant differences in outcome between the two groups.

## Disease-Free Survival

DFS (Figure 2b) did not differ significantly between treatment groups. The 5-year DFS 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=0.14). The unadjusted hazard ratio comparing the SLND-alone group to the ALND group was 0.82 (95% CI, 0.58–1.17), and the hazard ratio adjusted for adjuvant treatment and age was 0.88 (95% CI, 0.62–1.25) (Table 3). The adjusted hazard ratios comparing the SLND-alone group to the ALND group in the other multivariable models ranged from 0.84 to 0.89 (Table 3), all similar to the unadjusted rate of 0.82. LRR and its correlates have been previously reported.[33] The 5-year rates of local recurrence were

1.6% (95% CI: 0.7–3.3) and 3.1% (95% CI: 1.7–5.2) in the SLND-alone and ALND groups, respectively (p=0.11). Locoregional recurrence-free survival at 5 years was 96.7% (95% CI, 94.7%–98.6%) and 95.7% (95% CI, 93.6%–97.9%) in the SLND-alone and ALND groups, respectively (p=0.28).

## Discussion

In the ACOSOG Z0011 randomized trial, ALND did not significantly affect OS or DFS of patients who had clinical T1–T2 breast cancer and a positive SLN and were treated with lumpectomy, adjuvant systemic therapy, and tangential field whole-breast RT. These survival findings are consistent with those of the NSABP B04 trial in which clinically node-negative women 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 up to 25 years of follow-up, no statistically significant survival differences were observed. 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 since an axillary recurrence after SLND in patients with a lower risk of death from distant disease might negatively impact survival. The findings from Z0011 document the high rate of locoregional control achieved with modern multimodality therapy, even without ALND. In contrast to B04 where 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 OS was only about 60%, 100% of patients in Z0011 had nodal involvement; yet the 5-year OS was over 90%. Further, 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 of Z0011.[33] The excellent local and distant outcomes in this study highlight the impact of multiple changes in breast cancer management during the interval between the two studies. These changes, which include improved imaging, more detailed pathologic evaluation, improved planning of surgical and radiation approaches, and more effective systemic therapy, emphasize the need for ongoing re-evaluation of “standard” local therapy.

The well-documented morbidity from ALND has led other investigators to explore alternative methods of axillary treatment in clinically node-negative patients, including radiation, systemic therapy, and axillary observation. These have consistently demonstrated low axillary failure rates with no significant differences in survival.[3435] The International Breast Cancer Study Group trial of ALND versus observation is noteworthy because more than half 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 OS was 73% at a median follow-up of 6.6 years.[36]

The low rates of LRR at 5 years and the nearly identical OS and DFS between treatment groups in ACOSOG Z0011 would suggest that differences in survival between study groups are unlikely to emerge with longer follow-up since ALND would only affect survival by virtue of improved locoregional control. In the EBCTCG overview, statistically significant survival differences between treatments at 15 years were seen only when differences in LRR 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 NSABP 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] Since the total LRR rate in the Z0011 SLND-alone group at 5 years is only 2.5% compared to 3.6% in the ALND group, it is extremely 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 OS between the treatment groups in Z0011 is 0.7%, numerically favoring the SLND-alone group. The hazard ratio for OS comparing the SLND-alone group to the ALND group was 0.78 with a 90% CI of 0.56–1.10. The worst hazard ratio (1.10) is less than the 1.30 which was hypothesized as the maximum acceptable inferiority margin. In essence, this means that the 5-year OS for the SLND-alone group might be as low as 90.3% if the true 5-year OS for the ALND group was 91.8% and the hazard ratio is as high as 1.10. Most importantly, there is no suggestion that LRR rates, 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 suffer 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 H&E-detected metastases 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 RT followed by systemic therapy do not benefit from the addition of ALND in terms of local control, DFS, or OS. 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. Since 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.

Patients not included in the Z0011 trial are those undergoing mastectomy without radiotherapy, patients treated with partial-breast irradiation, patients receiving neoadjuvant therapy, and those receiving whole-breast irradiation in the prone position where 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 H&E-detected metastasis in the SLN, and 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.

## Acknowledgments

Supported by funding from the U.S. National Cancer Institute to the American College of Surgeons Oncology Group (ACOSOG) Grant U10 CA 76001. We thank the ACOSOG staff, in particular the leadership of Heidi Nelson, M.D. (ACOSOG Group Co-Chair, Mayo Clinic, Rochester, MN), David Ota, M.D. (ACOSOG Group Co-Chair, Duke University, Durham, NC), and Samuel A. Wells, Jr, M.D. (Senior Clinician, National Cancer Institute, Bethesda, MD). All three of these physicians contributed to study design and/or manuscript review; none received compensation. We also thank all of the investigators and their site research teams. Finally, we wish to thank the brave patients with breast cancer who participated in this study and their caregivers. The first author of this manuscript, Dr. Armando Giuliano, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Karla V. Ballman performed and is responsible for the statistical analysis. All authors attest to the fidelity of the article with respect to the full protocol and statistical plan.

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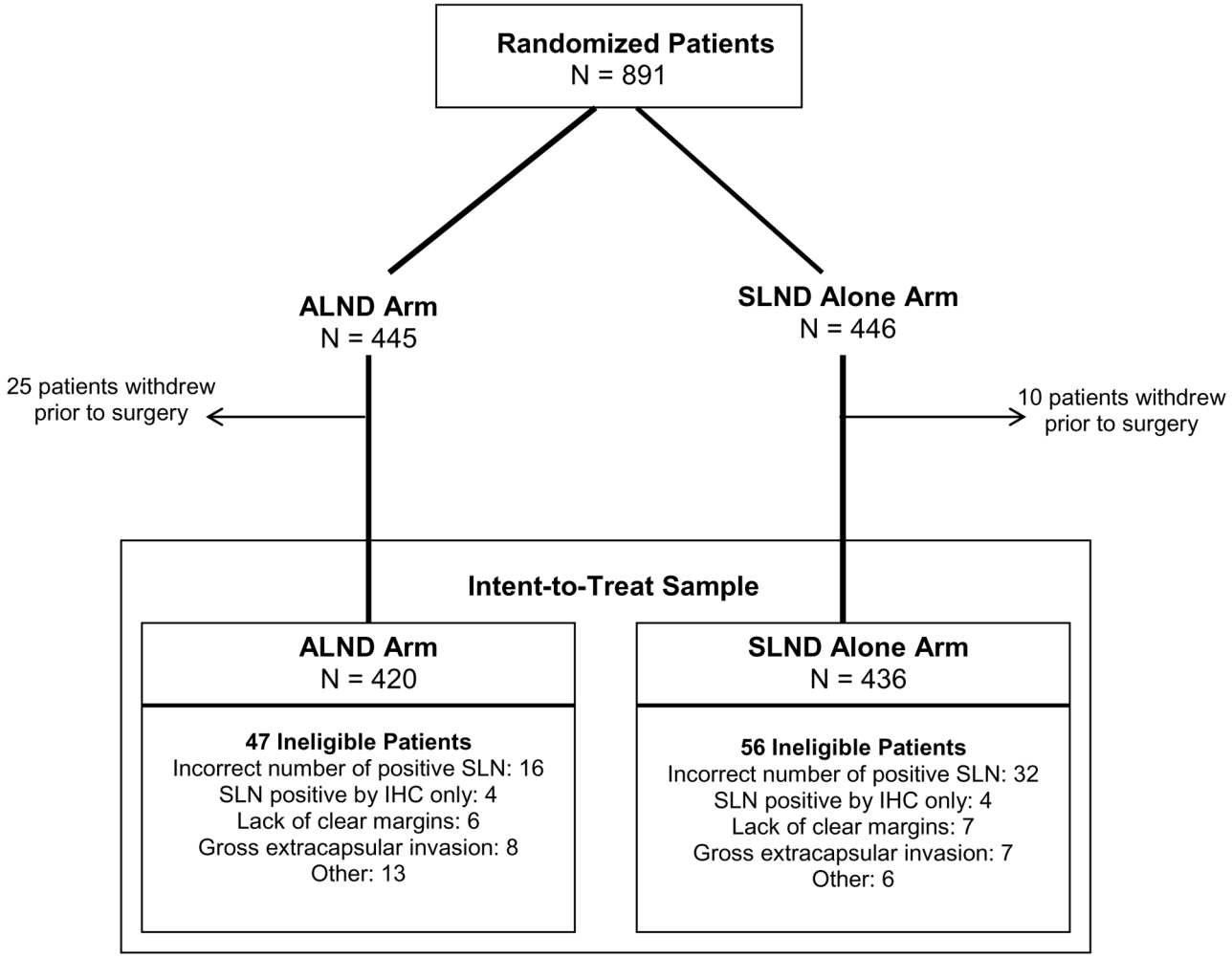
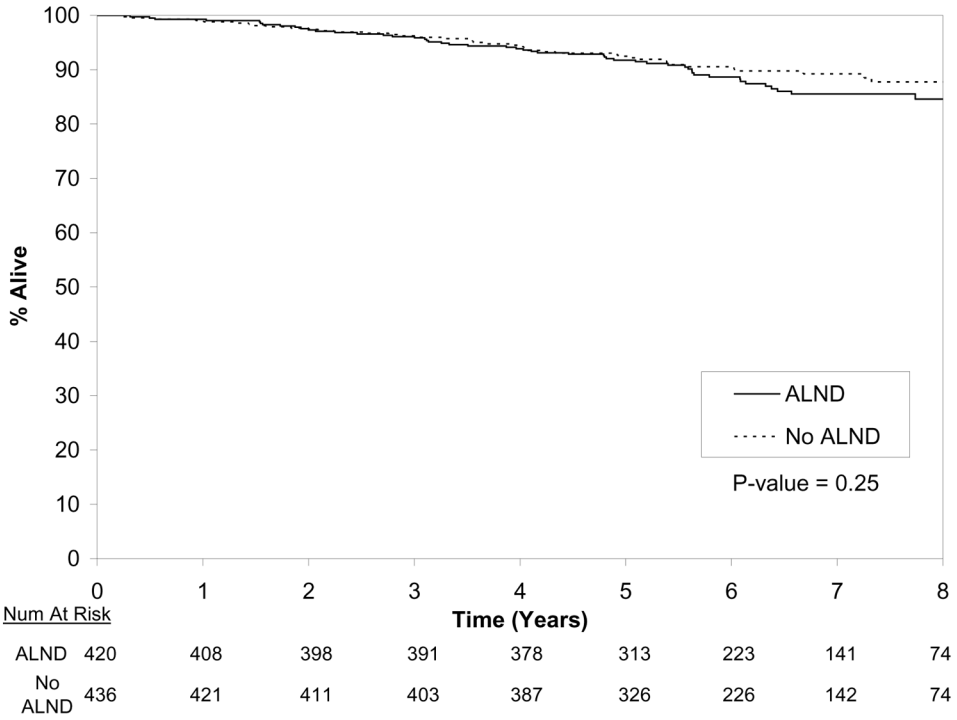



**Figure 1.**

CONSORT diagram for ACOSOG trial Z0011, A randomized trial of axillary node dissection in women with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node.

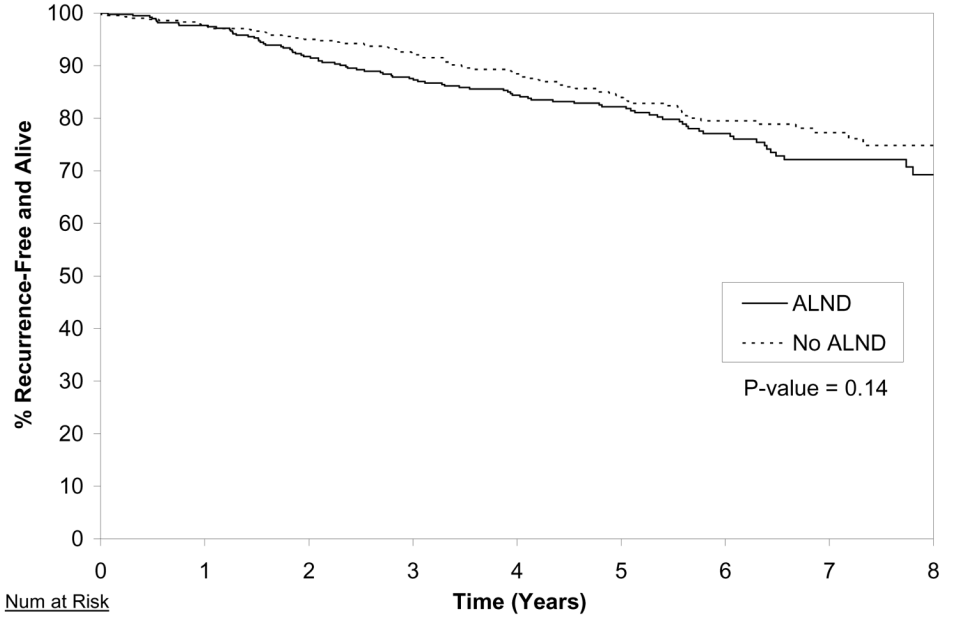
Figure 2a




Num At Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ALND | 420 | 408 | 398 | 391 | 378 | 313 | 223 | 141 | 74 |
| No ALND | 436 | 421 | 411 | 403 | 387 | 326 | 226 | 142 | 74 |

Figure 2b




Num at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ALND | 420 | 369 | 335 | 310 | 286 | 226 | 152 | 83 | 37 |
| No ALND | 436 | 395 | 363 | 337 | 307 | 231 | 147 | 81 | 36 |

**Figure 2.**

Figure 2a. Overall survival experience of the ALND group compared to the SLND-alone group (log-rank test).

Figure 2b. Disease-free survival experience of the ALND group compared to the SLND-alone group (log-rank test).

## Table 1

Baseline patient and tumor characteristics by study group

| | ALND group n = 420 | SLND-alone group n = 436 |
|---|---|---|
| **Age, years** | | |
| median (min, max) | 56 (24, 92) | 54 (25, 90) |
| missing | 7 | 10 |
| **Clinical T stage, n (%)** | | |
| T1 | 284 (67.9) | 303 (70.6) |
| T2 | 134 (32.1) | 126 (29.4) |
| missing | 2 | 7 |
| **Tumor size, cm** | | |
| median (min, max) | 1.7 (0.4, 7.0) | 1.6 (0.0, 5.0) |
| missing | 6 | 14 |
| **Receptor status, n (%)** | | |
| 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, n (%)** | | |
| yes | 129 (40.6) | 113 (35.2) |
| no | 189 (59.4) | 208 (64.8) |
| missing | 102 | 115 |
| **Modified Bloom-Richardson score, n (%)** | | |
| II | 71 (22.0) | 81 (25.6) |
| III | 158 (48.9) | 148 (46.8) |
| unknown | 94 (29.1) | 87 (27.5) |
| missing | 97 | 120 |
| **Tumor type, n (%)** | | |
| 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, n (%)** | | |
| 1 | 199 (58.0) | 295 (71.1) |
| 2 | 681 (19.8) | 76 (18.3) |
| 3 | 3 (7.3) | 11 (2.7) |
| 4 or more | 47 (13.7) | 4 (1.0) |

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

## Table 2

Adjusted hazard ratios for overall survival comparing the SLND-alone group to the ALND group. All the models are adjusted for the treatment group assignment, age, and whether or not the patient received adjuvant therapy.

| Model Variables | Number of Patients (Events) | Adjusted Hazard Ratio | 90% Confidence Interval | Non-inferiority p-value |
|---|---|---|---|---|
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no) | 839 (92) | 0.87 | 0.62, 1.23 | 0.028 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>Primary tumor size (cm, continuous) | 818 (92) | 0.89 | 0.62, 1.25 | 0.034 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>ER status (negative vs. positive) | 778 (87) | 0.92 | 0.64, 1.30 | 0.050 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>Modified Bloom-Richardson score (I vs. II vs. III) | 839 (92) | 0.86 | 0.61, 1.21 | 0.024 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>Tumor type (ductal vs. lobular vs. other) | 839 (92) | 0.88 | 0.63, 1.25 | 0.034 |

Abbreviations: ALND, axillary lymph node dissection; SLND, sentinel lymph node dissection; ER, estrogen receptor

## Table 3

Adjusted hazard ratios for disease-free survival comparing the SLND-alone group to the ALND group. All the models are adjusted for the treatment group assignment, age, and whether or not the patient received adjuvant therapy.

| Model Variables | Number of Patients (Events) | Adjusted Hazard ratio | 95% Confidence Interval* | p-value |
|---|---|---|---|---|
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no) | 839 (127) | 0.88 | 0.62, 1.25 | 0.47 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>Primary tumor size (cm, continuous) | 818 (125) | 0.86 | 0.60, 1.22 | 0.40 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>ER status (negative vs. positive) | 778 (117) | 0.84 | 0.58, 1.20 | 0.33 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>Modified Bloom-Richardson score (I vs. II vs. III) | 839 (127) | 0.87 | 0.61, 1.23 | 0.43 |
| Treatment group (SLND alone vs. ALND)<br>Age (≤ 50 vs. > 50 years)<br>Adjuvantly treated (yes vs. no)<br>Tumor type (ductal vs. lobular vs. other) | 839 (127) | 0.89 | 0.62, 1.27 | 0.52 |

Abbreviations: ALND, axillary lymph node dissection; SLND, sentinel lymph node dissection; ER, estrogen receptor