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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

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Abstract

Background and Objective—Sentinel lymph node dissection (SLND) has eliminated the need for axillary dissection (ALND) in patients whose sentinel node (SN) is tumor-free. However, completion ALND for patients with tumor-involved SNs remains the standard to achieve locoregional control. Few studies have examined the outcome of patients who do not undergo ALND for positive SNs. We now report local and regional recurrence information from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial.

Methods—ACOSOG Z0011 was a prospective trial examining survival of patients with SN metastases detected by standard H&E who were randomized to undergo ALND after SLND versus SLND alone without specific axillary treatment. Locoregional recurrence was evaluated.

Results—There were 446 patients randomized to SLND alone and 445 to SLND + ALND. Patients in the two groups were similar with respect to age, Bloom-Richardson score, estrogen receptor status, use of adjuvant systemic therapy, tumor type, T stage, and tumor size. Patients

randomized to SLND + ALND had a median of 17 axillary nodes removed compared to a median of only 2 SN removed with SLND alone ($P < 0.001$). ALND also removed more positive lymph nodes ($P < 0.001$). At a median follow-up time of 6.3 years, there were no statistically significant differences in local recurrence ($P = 0.11$) or regional recurrence ($P = 0.45$) between the two groups.

Conclusion—Despite the potential for residual axillary disease after SLND, SLND without ALND can offer excellent regional control and may be reasonable management for selected patients with early stage breast cancer treated with breast-conserving therapy and adjuvant systemic therapy.

Keywords

sentinel node; invasive breast cancer; axillary node dissection; locoregional recurrence

Introduction

Sentinel lymph node dissection (SLND) has revolutionized the management of clinically node-negative women with breast cancer. Single institutional studies, multi-institutional studies, and prospective randomized trials have shown the safety of omitting axillary lymph node dissection (ALND) for women whose sentinel node (SN) is free of metastatic disease.^{1–3} The recommended management, however, of the patient with SN metastases has continued to be completion ALND. ALND is advised because of its excellent regional control and potential impact on survival. Completion ALND for women with micrometastases or isolated tumor cells (ITCs) is especially controversial because of the uncertain clinical significance of micrometastases and the low yield of additional positive axillary lymph nodes. However, most consensus statements including one from the American Society of Clinical Oncology recommend ALND for patients whose SN contains macrometastases, ITCs, or micrometastases.^{4, 5}

A number of reports have suggested that selected patients with SN metastasis may be managed without completion ALND.^{6–8} However, most of these reports are small, single-institutional studies evaluating patients whose SN demonstrated primarily micrometastases or ITCs. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial entitled “A randomized trial of axillary node dissection in women with clinical T1 or T2 N0 M0 breast cancer who have a positive sentinel node” was designed to compare the overall survival of patients who had hematoxylin and eosin (H&E) detected metastases in their SN by SLND and were treated with completion ALND compared to patients managed without completion ALND or third field axillary radiation. The primary endpoint of the study was survival. However, locoregional control was assessed in order to determine the effect of ALND and SLND on these endpoints for contemporary women managed with breast-conserving surgery, adjuvant systemic therapy, and opposing tangential field whole breast irradiation. The results of this locoregional recurrence analysis are reported here. The locoregional recurrence rates seen in this study and the effect of the extent of operation on locoregional control provide important information regarding the management of the axilla for patients with early breast cancer.

Study Design and Methods

All participants were women at least 18 years of age with clinical T1 or T2 N0 M0 breast cancer treated with SLND and breast-conserving therapy as previously described.⁹ Lumpectomy margins were required to be negative for study participation. Planned mastectomy was not permitted. Patients must have undergone SLND within 60 days of the diagnosis of invasive breast carcinoma and have an ECOG/Zubrod status less than or equal to 2. A SN containing metastatic breast cancer must have been identified by frozen section, touch preparation or permanent section. Patients with metastatic breast cancer to the SN identified by immunohistochemical staining (IHC) were not eligible. Patients were randomized to completion ALND or no ALND and no further axillary-specific therapy, specifically no third field nodal irradiation. All patients received opposing tangential field whole breast irradiation. ALND was defined as an anatomic Level I and II dissection with at least 10 nodes removed. Adjuvant systemic therapy was determined by physician and patient selection. For patients randomized to completion ALND, the operation must have been performed within 42 days of the SLND. Pregnant or lactating patients were excluded as were patients treated with neoadjuvant chemo- or hormonal therapy. In addition, patients with bilateral breast cancer were excluded as were those with multicentric disease, a history of ipsilateral axillary surgery, pre-pectoral implants, or those with medical contraindications to ALND. Patients with matted nodes or gross extranodal disease at the time of SLND were excluded as were patients with three or more involved SNs.

Participants entered the study through two pathways, the most common of which was randomization post-SLND when the final histopathologic results of examination of the SN were known. However, some patients were pre-registered before SLND and then randomly assigned to a treatment arm intraoperatively by an interactive automated telephone system when frozen section or touch preparation analysis documented a tumor-involved SN. Although some of these patients were subsequently found to have three or more tumor-involved SNs, they were included in the analyses. All patients gave written informed consent, and all institutions obtained approval by their institutional review board. There were 165 investigators and 177 institutions participating in this study. Figure 1 illustrates the study schema.

Statistical Analysis

To validate reported data via source documentation, clinical site audits were performed according to the National Cancer Institute's Clinical Trials Monitoring Branch guidelines. The target accrual for the trial was 1900 patients in order to achieve a one-sided level of significance of 0.05 to detect a hazard ratio for overall survival of 1.3 (SLND only compared to ALND) with 90% power. Patients were randomized in a fashion that dynamically balanced three stratification factors: age (≤ 50 versus > 50 years), estrogen receptor status (positive versus negative), and tumor size (≤ 1 cm, > 1 cm but ≤ 2 cm, or > 2 cm). Patients were followed for disease-recurrence (local, regional, and distant) at 6, 12, 18, 24, 30, and 36 months following registration and then yearly until death or lost to follow-up. Time to locoregional recurrence was measured from the time of registration until the first of either a local or regional recurrence. Patients who were not known to have had a locoregional

recurrence at the time of analysis were censored at the date of their last follow-up. Patients who died without disease-recurrence were censored at the time of their death.

Chi-square tests were used to compare categorical variables between groups and two-sample t-tests were used to compare continuous variables between groups. Cox proportional hazards models were used to assess the univariable and multivariable association between prognostic variables, treatment, and locoregional recurrence. All statistical tests were two-sided and a p-value of 0.05 or less was considered statistically significant. Analyses were performed with SAS statistical analysis software, version 9.1 (SAS Institute, Cary, NC).

Results

Enrollment to Z0011 began in May 1999 with a planned accrual of 1900 patients. The trial was closed in December 2004 due to lower than expected accrual and event rates. There were 891 patients randomized with 35 patients (25 on the ALND arm and 10 on the SLND alone arm) excluded because they withdrew consent from the study. Eligible patients underwent lumpectomy and SLND alone or lumpectomy with SLND and completion ALND. Statistical analyses were performed on an intent-to-treat basis with 420 patients in the SLND + ALND arm and 436 in the SLND only arm. There were 43 (5.0%) patients who did not undergo their assigned treatment. Of the 420 patients assigned to the ALND arm, 32 (7.6%) did not undergo ALND and, of the patients who were assigned to the SLND alone arm, 11 (2.5%) had ALND. Figure 2 shows the trial participants by study arm (the intent-to-treat sample) and the number of patients who received ALND (388 patients) and SLND alone (425 patients) as originally assigned (the treatment received sample). The primary analyses were performed on the intent-to-treat sample, and all were repeated for the treatment received sample. Both analyses yielded similar results with no significant change in outcomes.

Within the intent-to-treat sample, there were 103 ineligible patients: 47 on the ALND arm and 56 on the SLND only arm. Reasons for ineligibility were: incorrect number of positive SNs (16 ALND arm and 32 SLND only arm), SNs positive by IHC only (4 ALND arm and 4 SLND only arm), positive lumpectomy margins (6 ALND arm and 7 SLND only arm), gross extracapsular extension in the SNs (8 ALND arm and 7 SLND only arm), and other (13 ALND arm and 6 SLND only arm). In both the intent-to-treat and treatment received samples, the two treatment arms were well balanced in terms of baseline patient and tumor characteristics (Table 1).

The number of lymph nodes removed and the extent of metastatic involvement for each study arm is presented in Table 2 with interquartile range (IQR) which reports the 25th and 75th percentile range. For the patients randomized to the ALND arm, the median total number of nodes removed was 17 (IQR: 13, 22). The median total number of histologically positive nodes identified in patients who underwent ALND was 1 (IQR: 1, 2). Among patients who underwent SLND alone, the median number of SNs removed was 2 (IQR: 1, 4). The median number of histologically positive nodes in the SLND alone arm was 1. As expected based on the randomization to ALND versus SLND alone, the distribution for the total number of nodes removed from patients who underwent ALND significantly differed

from the total number of nodes removed from patients who underwent SLND alone ($P < 0.001$). In addition, the number of patients with 2 or more positive nodes identified in the ALND group was 140 (40.8%) compared to 91 (21.9%) in the SLND only group. There were 3 or more positive nodes in 72 (21.0%) patients in the ALND group compared to 15 (3.6%) patients in the SLND alone group. There were 4 or more positive nodes in 47 (13.7%) patients in the ALND group compared to 4 (1.0%) in the SLND only group. In the ALND group, 97 (27.3%) of patients had additional metastasis in lymph nodes removed by ALND. Micrometastases were identified in SNs of 137 (37.5%) of patients in the ALND group compared to 164 (44.8%) in the SLND only group, ($P = 0.05$). Ten percent of patients with micrometastasis had additional involved nodes removed by ALND.

At a median follow-up of 6.3 years, locoregional recurrence was seen in only 29 (3.4%) of the entire population. Local recurrence was identified in only 8 (1.8%) of the SLND alone group compared to 15 (3.6%) in the ALND arm; the number (percent) of local recurrence at 5 years was 7 (1.6%) and 13 (3.1%) in the SLND only and ALND arms, respectively ($P = 0.11$). Regional recurrences in the ipsilateral axilla were similar between each arm with 4 (0.9%) patients in the SLND alone group compared to 2 (0.5%) in the ALND group. The median time of local recurrence-free survival and regional recurrence-free survival was not reached in either group and did not differ between the arms.

Locoregional recurrence was also evaluated by the treatment received arms. Sixteen (4.1%) locoregional recurrences were seen in 388 (89.0%) patients randomized to and treated with ALND compared to 12 (2.8%) locoregional recurrences seen in 425 (97.5%) patients randomized to and treated with SLND alone. Local recurrence was seen in 14 (3.6%) patients randomized to and treated with ALND compared to 8 (1.9%) patients randomized to and treated with SLND alone. Regional recurrence was seen in 2 (0.5%) patients randomized to and treated with ALND compared to 4 (0.9%) patients randomized to and treated with SLND alone. Similar to the intent-to-treat sample, there was no significant difference in the locoregional recurrence-free survival for the treatment received sample.

Adjuvant systemic therapy was delivered to 403 (96.0%) of patients in the ALND arm compared to 423 (97.0%) in the SLND only arm, ($P = 0.40$). Hormonal therapy was given to 195 (46.4%) of the patients in the ALND arm compared to 203 (46.6%) of patients in the SLND only arm, ($P = 0.97$). Chemotherapy was administered to 243 (57.9%) of patients in the ALND arm and 253 (58.0%) of patients in the SLND arm, ($P = 0.96$). The type of chemotherapy received by patients in the two groups was similar. The most common chemotherapeutic agents used in both arms were anthracycline and taxane-based combination chemotherapy regimens. Locoregional recurrence was seen in 3.3% of patients who did not receive adjuvant systemic therapy compared to 3.4% of patients who did receive adjuvant systemic therapy.

Prognostic factors that may predict locoregional failure were examined including estrogen receptor (ER) status, progesterone receptor (PR) status, pathologic tumor size, lymphovascular invasion, histologic type, size of SN metastases, total number of involved nodes, modified Bloom-Richardson score, adjuvant systemic therapy use, and patient age. Univariable analysis showed that only ER and PR status, pathologic tumor size, and

modified Bloom-Richardson score were associated with locoregional failure in either arm. Multivariable analysis showed that only modified Bloom-Richardson score and age were associated with locoregional failure. Table 3 shows univariable and multivariable analyses of predictors of locoregional failure.

Discussion

Breast cancer is currently diagnosed earlier than in the past, and the incidence and extent of axillary lymph node metastases have been decreasing.¹⁰ In patients with clinically node-negative disease, the SN is the only involved node in 40 to 60% of patients undergoing SLND.^{1, 11} Despite the increasing knowledge that many women will not have additional nodal metastases at completion ALND, the management of the patient with clinically negative, histologically positive lymph nodes has not changed, and ALND remains the gold standard. The hypothesis of the ACOSOG Z0011 trial was that patients with H&E-detected metastases in the SN would have similar outcomes whether they were randomized to completion ALND or no ALND and no axillary-specific irradiation. There was a remarkably low rate of locoregional recurrences among all patients on the Z0011 trial, even those who did not undergo ALND. No significant benefit in locoregional control was seen with completion ALND despite the removal of additional tumor-involved lymph nodes.

Currently, it is well accepted that the patient whose SN is tumor-free does not require further axillary-specific treatment. In a prospective randomized trial, Veronesi *et al.*³ demonstrated the overall safety of SLND alone compared to SLND followed by completion ALND for patients whose SN was free of metastatic disease. Their trial was a single-institution prospective study of 516 women with T1 tumors randomly assigned to either SLND + ALND or SLND alone. All patients underwent completion ALND if the SN contained metastatic disease. They found that women randomized to SLND alone had greater arm mobility and less pain than those who had both SLND + ALND. They recently reported an update with a median follow-up of 102 months¹² with only 49 breast cancer-related events in the entire cohort – 23 in the SLND alone arm and 26 in the SLND + ALND arm. Only 2 of 259 (0.77%) patients in the SLND alone arm experienced a regional recurrence. There was no significant difference between the two groups with respect to disease-free survival (89.9% in SLND arm compared to 88.8% in the SLND + ALND arm).

While current guidelines and most clinicians recommend ALND for women whose SN contains metastases, the enhanced detection of small volume metastases (micrometastases and ITCs) with SLND and enhanced pathologic assessment of the SN has led some to question the routine role of ALND in patients with early metastatic nodal disease. Several small studies have suggested that ALND may be safely omitted for patients with ITCs or micrometastases.^{6–8, 13} Ten to fifteen percent of patients whose SN is tumor-free by H&E staining have micrometastases detected by IHC.¹⁴ The ACOSOG Z0010 trial (“A prognostic study of sentinel node and bone marrow micrometastases in women with clinical T1 or T2 N0 M0 breast cancer”) blinded results of SN IHC analysis to clinicians in order not to influence treatment. Despite the fact that some of the women had occult SN metastases (and no specific axillary treatment), ACOSOG Z0010 reported regional recurrences at a rate of only 0.3%, with a median follow-up of 31 months.¹⁵

Several retrospective studies have been published reporting low axillary recurrence rates in women with positive SNs who did not have completion ALND for various reasons.^{6–8, 13, 16} These retrospective studies are limited by small size, limited knowledge of the reason why no ALND was performed, small volume SN metastases, and lack of controls. A review by Bilimoria *et al.*¹⁷ of the National Cancer Data Base identified 20.8% of 97,314 breast cancer patients with a positive SN who underwent SLND alone without completion ALND. There were no significant differences seen in axillary recurrences for patients who underwent SLND alone versus completion ALND. This retrospective database analysis revealed that patients who underwent SLND alone were older and had smaller tumors than those who had ALND.

Numerous authors have proposed methods of predicting the risk of additional positive axillary lymph nodes (non-SN) after SLND. Risk of additional non-SN metastases in patients with SN metastasis correlates with size of the primary tumor, size of the SN metastasis, number of SNs involved, lymphovascular invasion, and extranodal tumor extension.^{18, 19} Several nomograms have incorporated these prognostic features to predict the probability of additional involved non-SNs.^{20, 21} Proponents of the use of such nomograms postulate that axillary dissection should be necessary only if there are likely additional involved lymph nodes. They postulate that patients with residual nodal disease in the axilla should have a higher risk of regional recurrence than those patients with no residual disease who are unlikely to benefit from completion ALND. They assume that removal of residual axillary disease is beneficial.

Based on the finding that 27% of patients in the ALND arm of Z0011 had additional nodal metastases identified on histopathologic assessment of the axillary contents, patients randomized to the SLND alone arm of Z0011 were likely to have residual non-SN metastasis that was not removed by operation. As the regional recurrence rates were similar between the two groups, this study suggests that not all non-SN metastases develop into clinically detectable disease. Removal of additional involved nodes with ALND did not result in fewer locoregional recurrences than did SLND alone at a median follow-up time of 6.3 years. Traditionally, patients with invasive carcinoma of the breast underwent ALND to achieve accurate staging, regional control, and perhaps improved survival. Regional recurrence rates following ALND have been reported to be as low as 1 or 2%²²; however, ALND has significant morbidity and is costly. Its value in the era of early detection, increased use of breast-conserving surgery and adjuvant systemic therapy, and nodal assessment with SLND may be more limited than in the past. A number of randomized prospective trials have demonstrated that short- and long-term morbidity is lessened after SLND compared to ALND.^{9, 23} Therefore, if SLND could achieve locoregional control as effectively as ALND without an adverse effect on survival, it would be the preferable procedure.

There are limitations to the Z0011 trial which may have had an impact on the locoregional control for SN-positive women treated with or without ALND. Most of the patients in this trial had a low axillary tumor burden. Caution at the initiation of the study led to an attempt to assure that women with high tumor burden were not randomized to SLND alone and to minimize the threat of en cuirasse regional failure. Therefore, eligibility requirements

specified that when surgeons felt that there was extensive axillary disease upon palpation of the nodal basin during the SLND, they were required to exclude such patients by demonstrating three or more involved SNs. If a patient had three or more positive SNs, they were not eligible for randomization. Despite this requirement, there was a small proportion of patients with three or more positive SNs who did undergo randomization, 14 (3.4%) patients. Most of these patients were randomized intraoperatively prior to the knowledge of the total number of involved SNs. Another limitation of this trial is that although the detection of SN metastases was to be made based on standard H&E, not immunohistochemical detection, about 41% of study patients were ultimately determined to have small volume metastases (micrometastases or ITCs). This study was initiated when the 5th edition of the AJCC Cancer Staging Manual was in effect, and this iteration did not specify the subgroups of micrometastases or ITCs in the definition of nodal metastases. For this reason, we used method of detection, H&E, to identify SN metastases and did not stratify for volume of disease in the SN. However, the size of the SN metastases was recorded when known and the majority of patients were histopathologically N1.

Over 95% of patients in Z0011 received adjuvant systemic therapy. Adjuvant systemic therapy, both chemotherapy and hormonal therapy, is known to diminish locoregional recurrence in breast cancer patients.²⁴ In addition, all patients underwent breast-conserving surgery and were required to undergo whole breast irradiation. It is known that standard opposing tangential fields will irradiate the SLND operative field, much of the level I axilla, and a portion of the level II axilla. Schlembach *et al*²⁵ evaluated the volume of nodal radiation associated with breast-conserving therapy and noted that, by placing the deep field edge 2 cm below the chest wall/lung interface, the entire axillary dissection field site (Levels I and II) can be included in nearly all patients. Although no axillary-specific irradiation was performed in patients randomized on Z0011, it is likely that a significant portion of the axilla was treated in patients on both study arms due to the requirement for whole breast irradiation.

An early study of the National Surgical Adjuvant Breast and Bowel Project (NSABP), NSABP B-04²⁶, randomized clinically node-negative women to radical mastectomy, total mastectomy with axillary irradiation, or total mastectomy alone without axillary treatment. Thirty-eight percent of women whose axilla was dissected had nodal metastases whereas in the group with untreated nodal disease, less than half that number developed clinically evident axillary recurrence. Patients on the B-04 trial did not routinely receive adjuvant systemic therapy; therefore, no treatment effect could account for the lack of clinical progression of axillary nodal metastases in the group with no axillary treatment. This suggests that not all axillary metastases ultimately progress to become clinically evident.

The low locoregional recurrence rates in ACOSOG Z0011 show that locoregional control in patients with low to moderate axillary tumor burden treated with breast-conserving therapy and adjuvant systemic therapy may not be improved by ALND after SLND compared to SLND alone. This study particularly questions the use of ALND in women with immunohistochemically detected micrometastases or isolated tumor cells in the SN.

SLND provides the necessary staging information to direct adjuvant therapy and may be therapeutic as well. The results of this study are not applicable to women with palpable nodal disease, those in whom SLND reveals extensive metastases, or those undergoing mastectomy for treatment of the primary tumor. Although most axillary recurrences are evident within the first two or three years after surgery, the long-term results and the impact of the omission of ALND on survival remain to be seen.

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Z0011 Study Design Schema

Figure 1.
Study design showing randomization process

Figure 2.
Definition of the study sample depicting total number of randomized patients, number of patients in intent-to-treat sample, and number of patients in treatment received sample

Table 1

Characteristics of Patients and Primary Tumors in the 2 Study Arms

	Intent-to-Treat Sample		Treatment Received Sample	
	ALND arm N = 420	SLND only arm N = 436	ALND N = 388	SLND only N = 425
Age, years				
median (min, max)	56(24,92)	54(25,90)	56(24, 92)	54(25, 90)
missing	7	10	7	10
Age, years				
50, no. (%)	135(32.7)	160(37.6)	124 (32.6)	155 (37.4)
> 50, no. (%)	278(67.3)	266(62.4)	257 (67.4)	260 (62.6)
missing	7	10	7	10
Clinical T stage, no. (%)				
T1	284(67.9)	303(70.6)	259(67.1)	296(70.5)
T2	134(32.1)	126(29.4)	127(32.9)	124(29.5)
missing	2	7	2	5
Clinical tumor size, cm				
median (min, max)	1.7(0.4,7.0)	1.6(0.0,5.0)	1.8 (0.4, 6.0)	1.6 (0. 5.0)
missing	6	14	6	12
Receptor status, no. (%)				
ER+/PgR+	256(66.8)	270(68.9)	273(66.8)	264(68.9)
ER+/PgR–	61(15.9)	54(13.8)	54(15.2)	52(13.6)
ER–/PgR+	3(0.8)	4(1.0)	3(0.8)	4(1.0)
ER–/PgR–	63(16.5)	64(16.3)	61(17.2)	63(16.5)
missing	37	44	33	42
Estrogen Receptor, no. (%)				
ER+	327(83.0)	332(83.0)	301(82.2)	323(82.8)
ER–	67(17.0)	68(17.0)	65(17.8)	67(17.2)
missing	26	36	22	35
Progesterone Receptor, no. (%)				
PR+	260(67.7)	274(69.9)	241(67.7)	268(70.0)
PR–	124(32.3)	118(30.1)	115(32.3)	115(30.0)
missing	36	44	32	42
LVI *, no. (%)				
Yes	129(40.6)	113(35.2)	124(41.7)	111(35.6)
No	189(59.4)	208(64.8)	173(58.3)	201(64.4)
missing	102	115	91	113
Modified Bloom-Richardson score, no (%)				
I	71(22.0)	81(25.6)	64(21.3)	80(26.0)
II	158(48.9)	148(46.8)	147(49.0)	142(46.3)
III	94(29.1)	87(27.5)	89(29.7)	85(27.7)
missing/unknown	97	120	88	118

	Intent-to-Treat Sample		Treatment Received Sample	
	ALND arm N = 420	SLND only arm N = 436	ALND N = 388	SLND only N = 425
Tumor type, no. (%)				
Infiltrating ductal	344(82.7)	356(84.0)	317(82.1)	347(84.0)
Infiltrating lobular	27(6.5)	36(8.5)	25(6.5)	35(8.5)
Other	45(10.8)	32(7.5)	44(11.4)	31(7.5)
missing	4	12	2	12

*
LVI, Lymphovascular invasion

Table 2

Number and extent of disease of lymph nodes by treatment arm for the intent-to-treat and the treatment received samples.

	Intent-to-Treat Sample		Treatment Received Sample		<i>P</i>
	ALND (N = 420)	SLND only (N = 436)	ALND (N = 388)	SLND only (N = 425)	
Total number of nodes removed					<0.001
median	17	2	17	2	
IQR*	13,22	1,4	13,22	1,3	
Number of positive nodes, no.(%)					
0	4(1.2)	29(7.0)	3(0.88)	28(6.9)	<0.001
1	199(58.0)	295(71.1)	198(58.1)	290(71.8)	
2	68(19.8)	76(18.3)	68(19.9)	74(18.3)	
3	72(21.0)	15(3.6)	72(21.1)	12(3.0)	
Unknown	77	21	47	21	
Size of SN Mets, no. (%)					
Micro	137(37.5)	164(44.8)	120(35.4)	160(44.6)	0.02
Macro	228(62.5)	202(55.2)	219(64.6)	199(55.4)	
Unknown	55	70	49	66	

* IQR is the Interquartile range, which is the 25th percentile, 75th percentile

Table 3

Univariable and multivariable associations of prognostic factors with locoregional recurrence for the intent-to-treat sample.

		Univariable p	HR (CI) (univariable)	Multivariable p (all variables)	HR (CI) (all variables)
ER Status					
	Negative	0.0002	0.229 (0.106, 0.496)	0.6244	0.707 (0.176, 2.837)
	Positive				
PR Status					
	Negative	0.0207	0.410 (0.193, 0.873)	0.3724	0.501 (0.110, 2.289)
	Positive				
Pathologic Tumor Size					
	Path tum size	0.0012	1.242 (1.090, 1.416)	0.4686	1.085 (0.870, 1.353)
Lymphovascular Invasion					
	Yes	0.1832	0.559 (0.237, 1.316)	0.4405	0.652 (0.219, 1.935)
	No				
Histologic Type					
	Ductal	---	---	---	---
	Lobular	0.9848	0.000 (0.000, .)	0.9952	0.000 (0.000, .)
	Other	0.3060	0.353 (0.048, 2.593)	0.9953	0.000 (0.000, .)
Sentinel Node Met Size					
	Micro	0.3080	0.670 (0.311, 1.446)	0.4255	0.620 (0.191, 2.010)
	Macro				
# Positive Total LN					
	0	0.5335	1.160 (0.727, 1.852)	0.2948	1.505 (0.700, 3.234)
	1				
	2				
	3 or more				
Modified Bloom-Richardson Score					
	I	0.0002	6.105 (2.385, 15.622)	0.0258	3.536 (1.165, 10.733)

		Univariable p	HR (CI) (univariable)	Multivariable p (all variables)	HR (CI) (all variables)
	II				
	III				
Adjuvant Systemic Therapy					
	No	0.1687	0.583 (0.270, 1.257)	0.1281	0.429 (0.144, 1.276)
	Yes				
Age					
	≤50	0.0421	0.468 (0.225, 0.973)	0.0260	0.285 (0.095, 0.861)
	>50				
Arm					
	ALND	0.2802	0.666 (0.318, 1.394)	0.7411	0.825 (0.263, 2.586)
	SLND only				