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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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 Z0011 trial.

Methods: American College of Surgeons Oncology Group Z0011 was a prospective trial examining survival of patients with SN metastases detected by standard H and 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 2 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 with 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 2 groups.

Conclusions: 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.

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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 outcomes of patients whose hematoxylin and eosin (H and E)-detected SN metastases were treated with completion ALND or managed without completion ALND and without third field axillary radiation. The primary end point of the study was overall survival. Although locoregional recurrence was not a prespecified secondary end point, the study did have a prespecified plan for monitoring regional recurrence, reflecting concern that regional recurrence rate might be unacceptably high without completion ALND. Thus, locoregional control was assessed to determine the effect of ALND and SLND in contemporary women managed with breast-conserving surgery, adjuvant systemic therapy, and opposing tangential field whole breast irradiation. 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 Eastern Cooperative Oncology Group

(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, prepectoral 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 3 or more involved SNs.

Participants entered the study through 2 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 preregistered 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 3 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.

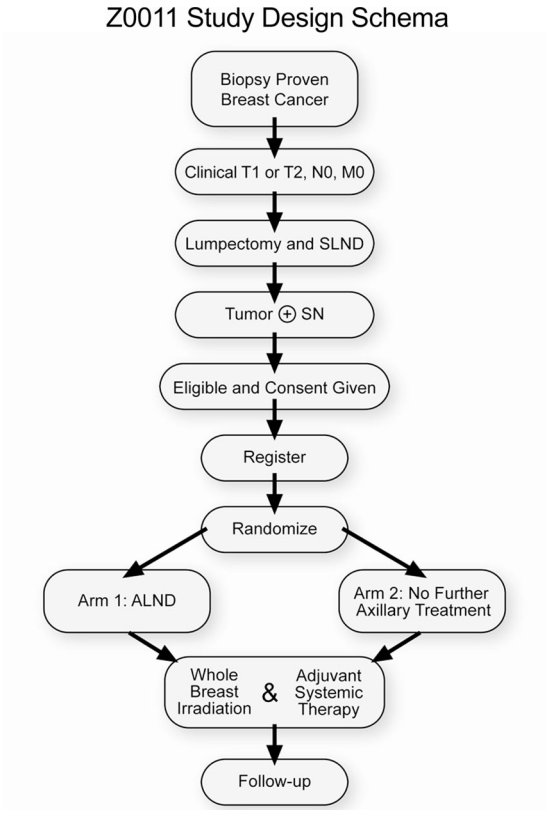

FIGURE 1. Study design showing randomization process.

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 to achieve a 1-sided level of significance of 0.05 to detect a hazard ratio for overall survival of 1.3 (SLND only compared with ALND) with 90% power. Patients were randomized in a manner that dynamically balanced 3 stratification factors: age ($\leq$50 vs. $>$50 years), estrogen receptor status (positive versus negative), and tumor size ($\leq$1 cm, $>$1 cm but $\leq$2 cm, or $>$2 cm). Patients were followed up 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. Local recurrence was defined as any ipsilateral in-breast recurrence; regional recurrence was defined as recurrence in the axillary, supraclavicular or internal mammary nodes. 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.

χ^2 tests were use to compare categorical variables between groups and 2-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 2-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 2 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

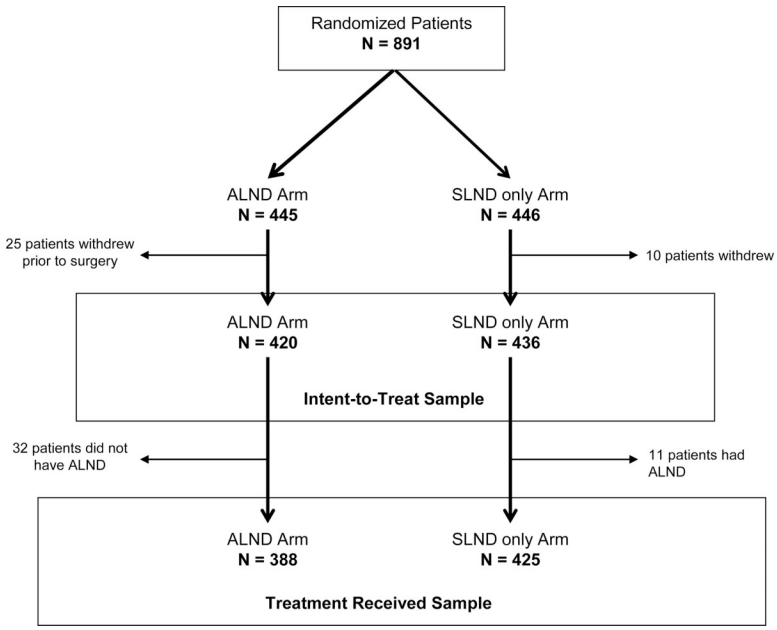

FIGURE 2. Definition of the study sample depicting total number of randomized patients, number of patients in intent-to-treat sample, and number of patients in treatment received sample.

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 removed nodes was significantly different between patients who underwent ALND and 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 with 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 with 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 with 4 (1.0%) in the SLND only group. In the ALND group, 97 (27.3%) patients had additional metastasis in lymph nodes removed by ALND. Micrometastases were identified in SNs of 137 (37.5%) patients in the ALND group compared with 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%) patients of the entire population. Local recurrence was identified in only 8 (1.8%) of the SLND alone group compared with 15 (3.6%) in the ALND arm; the number of local recurrences 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 with 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. Sixteen (4.1%) locoregional recurrences were seen in 388 (89.0%) patients randomized to and treated with ALND compared with 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 with 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 with 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 with 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 with 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 2 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 with 3.4% of patients who did receive adjuvant systemic therapy.

Prognostic factors that may predict locoregional failure were examined including estrogen receptor status, progesterone receptor 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 estrogen receptor and progesterone receptor 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 increasing evidence that many women will not have additional nodal metastases at completion ALND, the management of

TABLE 1. Characteristics of Patients and Primary Tumors in the 2 Study Arms

	Intent-to-Treat Sample		Treatment Received Sample	
	ALND (N = 420)	**SLND Only (N = 436)**	**ALND (N = 388)**	**SLND Only (N = 425)**
Age, yr				
Median (min, max)	56 (24, 92)	54 (25, 90)	56 (24, 92)	54 (25, 90)
Missing	7	10	7	10
Age, yr				
≤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
Tumor type, no. (%)				
Infiltrating ductal	344 (82.7)	356 (84.0)		347 (84.0)
Infiltrating lobular	27 (6.5)	36 (8.5)	317 (82.1)	35 (8.5)
Other	45 (10.8)	32 (7.5)	25 (6.5)	31 (7.5)
Missing	4	12	44 (11.4)	12

LVI indicates lymphovascular invasion; ALND, axillary lymph node dissection; SLND, sentinel lymph node dissection; ER, estrogen receptor; PgR, progesterone receptor.

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 and 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 with 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 +

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		
	ALND (N = 420)	SLND Only (N = 436)	*P*	ALND (N = 388)	SLND Only (N = 425)	*P*
Total no. nodes removed						
Median	17	2	<0.001	17	2	<0.001
IQR*	13, 22	1, 4		13, 22	1, 3	
Positive nodes, no.(%)						
0	4 (1.2)	29 (7.0)	<0.001	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 metastasis, no. (%)						
Micro	137 (37.5)	164 (44.8)	0.05	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.
ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection; SN, sentinel node.

ALND. They recently reported an update with a median follow-up of 102 months,[12] 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 2 groups with respect to disease-free survival (89.9% in SLND arm compared with 88.8% in the SLND + ALND arm).

Although 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 and 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 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 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 2 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 with 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

TABLE 3. Univariable and Multivariable Associations of Prognostic Factors With Locoregional Recurrence for the Intent-to-Treat Sample

	Univariable *P*	Hazard Ratio (CI) (Univariable)	Multivariable *P* (All Variables)	Hazard Ratio (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	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 metastasis size				
Micro	0.3080	0.670 (0.311, 1.446)	0.4255	0.620 (0.191, 2.010)
Macro				
No. positive total lymph nodes				
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)
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				

CI indicates confidence intervals; ER, estrogen receptor; PR, progesterone receptor; ALND, axillary lymph node dissection; SLND, sentinel lymph node dissection.

demonstrating 3 or more involved SNs. If patients had 3 or more positive SNs, they were not eligible for randomization. Despite this requirement, a small proportion of patients with 3 or more positive SNs 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 and 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 and 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 because of the requirement for whole breast irradiation.

An early study of the National Surgical Adjuvant Breast and Bowel Project (NSABP), NSABP B-04,[26] 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 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 with SLND alone. This study particularly questions the use of ALND in women with immunohistochemically detected micrometastases or ITCs 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 2 or 3 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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Discussions

DR. BLAKE CADY (BROOKLINE, MA): The message from ACOSOG Z-11 is contemporary reaffirmation of Dr. Fischer's 1970s B-04 trial of palpable breast cancers with a 40% rate of axillary nodal metastases: Not all known axillary metastases recur clinically if only observed. This Z-11 trial of contemporary smaller breast cancers, many nonpalpable, but all defined by sentinel node metastases, shows that axillary dissection may not be necessary nowadays for preventing regional node recurrences. Z-11 results also call into question the many nomograms for predicting nonsentinel node metastases after a positive sentinel node biopsy, which induce axillary dissections, as current guidelines mandate.

Once axillary node metastases are defined by sentinel node biopsy, information for systemic adjuvant therapy is adequate, without the need for harvesting more nodes, since regional node control is achieved, and systemic therapies are not usually, or should not be, governed by the number of node metastases, but only by sentinel macrometastases.

We can now reduce to a minimum surgical morbidity after breast conservation. Axillary dissection accomplishes nothing for T1, T2, clinically N0 breast cancers for regional control, yet can produce prolonged morbidity.

Z-11 results can also be extrapolated to overall survival, in my estimation, since 8-year locoregional disease-free survival was equivalent comparing axillary dissection to observation for positive sentinel nodes.

We published 2 extensive literature reviews of trials of variations in regional nodal surgery in gastric, esophageal, pulmonary, colorectal, breast cancers, and melanoma. Overall survival is not altered by super-radical, radical, modified, or minimal nodal surgery, or by observation only. If one cannot improve survival by variations of nodal surgery, how can survival be improved by taking out more and more negative lymph nodes, a current surgical enthusiasm, except as a manifestation of stage shifting—the "Will Rogers" phenomena.

Thus, lymph node metastases are indicators, not governors, of survival. Treatment variations are not even related to regional control in the great majority of modern breast cancers, with a median diameter of only 1.5 cm and few node metastases.

The counterintuitive truth of the lack of relationship between nodal treatment and overall survival can be understood by the research of Josh Fidler and others that elaborate the organ-specificity of metastatic disease. Liver and lung oligometastases are successfully resected because liver- and lung-specific metastatic cells possess no ability to grow in other organs. Likewise, lymph-node-specific metastases shed nodal-specific cells that are unable to grow in vital organs, and thus do not control survival.

Let us celebrate ACOSOG and its many trials, so imaginatively conceived by Sam Wells. Z-11, carried forward by Dr. Giuliano and his colleagues, has demonstrated a newer biologic understanding of regional node metastatic behavior and its relationship to multiple outcomes.

My questions are—First, do you think it necessary to repeat the underpowered Z-11 trial that might now meet recruitment goals to further solidify your findings? Second, will you now avoid axillary dissection, even if the sentinel node shows metastases? And if so, why should you, or any surgeon, do frozen sections of sentinel nodes, because it will make no difference in selection of further axillary surgery, regional node control, or overall survival?

Dr. Kelly McMasters (Louisville, KY): Do you consider the results of the study to be standard-of-care changing? Second, I wanted to ask whether the results of your study are applicable to other patient populations, such as those who undergo mastectomy instead of lumpectomy and radiation therapy; to those who undergo partial breast irradiation, as opposed to whole-breast irradiation; and to those with T3 cancers.

Dr. Michael Choti (Baltimore, MD): One must assume, based on these findings, that 25% or so of patients had residual, presumably viable tumor, in the axilla, and yet less than 1% developed regional recurrence. How do you explain this paradox? Do you think that disease is still present, is it biologically indolent, as perhaps Dr. Cady suggested, or do you think it is the adjuvant chemotherapy or radiation therapy that may have sterilized the axilla?

CLOSING DISCUSSANT

Dr. Armando Giuliano (Santa Monica, CA): I will start with Dr. McMasters' questions. First, is this standard of care? I think any study is a sample. These results are only applicable to patients with qualifications making them eligible for the trial—that is, clinically node negative, T1, T2, treated with breast-conserving therapy, et cetera. Results are not applicable to those treated with mastectomy because mastectomy patients usually do not receive opposing tangential field radiation. Partial breast irradiation was not permitted in this trial, so I do not think these results should be applied to those patients. Patients with T3 cancers were also excluded; so I would not apply these results to those patients, either.

Dr. Choti pointed out what makes these results so troubling. We know that patients have residual disease that was not removed, and yet the disease did not grow. NSABP B-04, which was conducted in the 70s, studied patients treated with no adjuvant systemic therapy, and there was an arm of the trial on which patients were treated without axillary dissection, without axillary radiation; without any axillary treatment. The regional recurrence in that arm was half of what you would have expected from the number of patients with lymph node metastases seen in the axillary dissection arm. Thus, there are biologic factors related to the progression of axillary disease that we do not understand. NSABP B-04 patients had palpable cancer, not detected on screening, which is a much different cancer, probably more aggressive than those seen in our study. Yet, axillary disease did not progress.

As Dr. Cady said, the spread of disease from the axilla may not be what is affecting survival.

In addition, contemporary patients who get opposing tangential field irradiation get radiation therapy to nearly the entire axilla; so they are, in fact, treated. Nearly all, 96%, received adjuvant systemic therapy, which also diminishes locoregional failure.

These factors may explain these counterintuitive results. The results presented are what we observed, but we cannot be certain of the reasons for these observations.

It would have been nice to have achieved our target accrual. But because of the extraordinarily low event rate, our target accrual may not have been enough to show noninferiority, which is how the trial was designed.

However, this is the largest randomized study of patients with positive sentinel lymph nodes treated with or without an axillary lymph node dissection. It is unlikely to be repeated in this country. Nor do I think it is necessary to repeat it. What is important is not that we failed to show equivalency, but that we showed an extraordinarily low locoregional failure without axillary lymph node dissection.

When a study does not achieve the target accrual, it is helpful to look at the 95% confidence intervals. In this case, for sentinel node biopsy alone, the 95% confidence interval is 0.32 to 1.39. Therefore, in the worst case scenario, sentinel node biopsy alone would have a regional recurrence of about 1 and a third times higher than axillary dissection, which would make it slightly above 1%. In the best case scenario, it is only one-third of the recurrence rate of axillary dissection.

The question then becomes: "Is an axillary dissection worth avoiding a 1% regional recurrence?" I think not.

I have avoided using frozen section on sentinel nodes for many years because I like to discuss the implications of the findings in the sentinel node with the patient and discuss the pros and cons of further axillary dissection. I have not performed axillary dissection for most patients with ITCs or micrometastases.

We are currently meeting with our multidisciplinary group to decide how we want to use the results of this study. It seems to me it is inescapable that axillary dissection in most women, such as the women in this cohort of patients, is not necessary to achieve locoregional control.

I do think we will have to examine the impact on survival, which we are currently analyzing, before we can totally abandon the operation. However, I think the role of axillary dissection must be reanalyzed and perhaps eliminated in the management of most women with contemporary breast cancer.