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Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients with Sentinel Lymph Node Metastases: Long-Term Follow-Up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial

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Abstract

Background and Objective—The early results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated no difference in locoregional recurrence for patients with positive sentinel lymph nodes (SLN) randomized either to axillary lymph node dissection (ALND) or SLN dissection (SLND) alone. We now report long-term locoregional recurrence results.

Methods—ACOSOG Z0011 prospectively examined overall survival of patients with SLN metastases undergoing breast-conserving therapy randomized to undergo ALND after SLND or no further axillary specific treatment. Locoregional recurrence was prospectively evaluated and compared between the groups.

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Results—Four hundred forty-six patients were randomized to SLND alone and 445 to SLND plus ALND. Both groups were similar with respect to age, Bloom-Richardson score, ER status, adjuvant systemic therapy, histology, and tumor size. Patients randomized to ALND had a median of 17 axillary nodes removed compared to a median of only 2 SLNs removed with SLND alone ($P < 0.001$). ALND, as expected, also removed more positive lymph nodes ($P < 0.001$). At a median follow-up of 9.25 years, there was no statistically significant difference in local recurrence-free survival (P=0.13). The cumulative incidence of nodal recurrences at 10 years was 0.5% in the ALND arm and 1.5% in the SLND alone arm (P=0.28). Ten-year cumulative locoregional recurrence was 6.2% with ALND and 5.3% with SLND alone (P=0.36).

Conclusion—Despite the potential for residual axillary disease after SLND, SLND without ALND offers excellent regional control for selected patients with early metastatic breast cancer treated with breast-conserving therapy and adjuvant systemic therapy.

Introduction

SLND alone is widely accepted as axillary management for women with clinically node-negative breast cancer. However, SLND without axillary lymph node dissection (ALND) for selected SLN-positive patients remains controversial even though two prospective randomized trials have demonstrated non-inferiority of SLND alone to SLND + ALND for SLN-positive patients.[1-3] The first such trial reported, the American College of Surgeons Oncology Group (ACOSOG) Z0011, “A Randomized Trial of Axillary Node Dissection in Women With Clinical T1-2 N0-1 M0 Breast Cancer Who Have a Positive Sentinel Node,” investigated outcomes for patients with hematoxylin and eosin (H&E)-detected metastatic disease who were treated with SLND alone. When ACOSOG Z0011 was initially reported with a median follow-up of 6.3 years, regional recurrence after SLND alone for women with axillary metastases was surprisingly low (0.9%), and ALND after SLND did not significantly diminish regional recurrence or improve survival.[1, 2] The International Breast Cancer Study Group reported similar results in a study of patients with micrometastases in the sentinel node.[3]

The initial report of ACOSOG Z0011 was embraced by some but criticized by others for inadequate follow-up. Critics felt the 6.3 years’ median follow-up was insufficient to permit abandonment of the time-honored technique of ALND for patients with axillary metastases. However, the findings of the study are not without historical precedent. The National Surgical Adjuvant Breast Project (NSABP) B-04 trial that began over 40 years ago showed that ALND did not improve survival in node-positive women whose axilla was not dissected at presentation despite a high probability of axillary nodal metastases.[4] In that study, clinically node-negative patients had palpable disease in the breast and received no adjuvant systemic therapy. Despite that, the number of axillary recurrences in the group of patients who did not have an ALND was only approximately half of what was anticipated from the number of patients who had metastases in the ALND group. However, most patients had tumor-free axillary lymph nodes, resulting in too small a number of positive-node patients to clearly identify the role of ALND for clinically node-negative but pathologically node-positive women treated without ALND.

The purpose of the ACOSOG Z0011 trial was to compare outcomes of a larger group of patients with sentinel node metastases detected by H&E staining and treated with breast-conserving therapy and contemporary adjuvant systemic therapy with or without ALND and without third field axillary irradiation. The inclusion of only patients undergoing breast-conserving therapy was due to the recognition that opposing tangential field irradiation often treats low axillary nodes. The primary endpoint of Z0011 was overall survival. However, the study had a pre-specified plan for monitoring regional and local recurrence, reflecting concern that the regional recurrence rate may be unacceptably high for women with undissected axillary metastases. Thus, locoregional control was assessed prospectively and carefully monitored to determine the effect of SLND with and without ALND on locoregional outcomes. The low locoregional recurrence rates seen in the initial report of the study provided reassuring evidence that locoregional recurrence rates were sufficiently low to abandon ALND. However, most patients had estrogen-receptor positive tumors which are known to recur over a prolonged period of time, even after five years[5], and the occurrence of late regional recurrences was a concern. We now report the 10-year locoregional recurrence rates (LRR) among these node-positive women treated with or without ALND.

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.[1, 2] 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. An SLN containing metastatic breast cancer must have been identified by frozen section, touch preparation, or permanent section without the use of immunohistochemistry (IHC). Patients with metastatic breast cancer to the SLN identified by IHC staining were not eligible. Patients were randomized to completion ALND or no ALND after SLND and no further axillary-specific therapy. The protocol specified no third field nodal irradiation. All patients were to receive 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 choice. Pregnant or lactating patients were excluded as were patients treated with neoadjuvant hormonal or chemotherapy. In addition, patients with bilateral breast cancers 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 extension at the time of SLND were excluded as were patients with 3 or more involved SLNs. The protocol did not require removal of three or more SLN, but in order to exclude patients felt to have “extensive nodal disease” intraoperatively, surgeons were given the option to exclude such patients by documenting at least three nodes involved with metastasis.

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 SLN 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 SLNs, they were included in the analyses. All patients gave written informed consent, and all institutions obtained approval by their respective institutional review boards. 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 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 on three stratification factors: age (≤ 50 versus > 50 years), estrogen receptor status (positive versus negative), and tumor size (≤1cm, > 1 cm or ≤ 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 a 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. Cumulative incidence of locoregional recurrence was summarized with the Kaplan-Meier estimator and was compared using a log-rank test. 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. All analyses were done on an intent-to-treat population and repeated for the treatment-received population. Analyses were performed with SAS statistical analysis software, version 9.3 (SAS Institute, Cary, NC) by Alliance statisticians on a dataset locked on 11/17/15.

RESULTS

As previously reported[1, 2], 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 followed by completion ALND. The intent-to-treat sample had 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. 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. The intent-to-treat analyses are reported here.

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 have been previously reported. 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 are presented in Table 2. 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 SLNs removed was 2 (IQR: 1,4). The median number of histologically positive nodes in the SLND alone arm was 1 (IQR: 1,1). As expected, the total number of removed nodes and total number of involved nodes were significantly higher in patients who underwent ALND compared to those patients who underwent SLND without ALND ($P < 0.001$ for both). In the ALND group, 97 (27.3%) patients had additional metastasis in lymph nodes removed by ALND. Micrometastases were identified in SLNs 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 SLN micrometastasis had additional macrometastasis in involved nodes removed by ALND, and these patients were considered to have macrometastases.

At a median follow-up of 9.25 years, locoregional recurrence was seen in only 39 patients in the entire population. One local recurrence in the SLND only arm occurred after 10 years. The cumulative incidence of local recurrences at 10 years was 19 (5.6%) and 12 (3.8%) in the ALND and SLND only arms, respectively ($P = 0.13$). Cumulative incidence of regional recurrences at 10 years in the ipsilateral axilla were similar between each arm with 2 (0.5%) in the ALND group compared with 5 (1.5%) patients in the SLND alone group. The cumulative incidence of locoregional recurrence did not differ between the arms ($P = 0.36$): 10-year cumulative locoregional incidence was 6.2% and 5.3% for the ALND and SLND only arms, respectively (Figure 2). The median time of locoregional, regional, and local recurrence was 3.1 years, 4.0 years, and 3.1 years respectively. Table 3 summarizes the cumulative incidence of locoregional recurrences at specific timepoints. In the SLND alone arm, only 1 patient experienced a regional recurrence after the 76 months of initial follow-up and only 1 patient experienced a local recurrence after 10 years.

Adjuvant systemic therapy was delivered to 403 (96.0%) 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%) patients in the ALND arm and 253 (58.0%) 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.

Prognostic factors that may predict locoregional failure were examined including hormone receptor status (negative if both the estrogen receptor and progesterone receptor status were negative, otherwise positive), pathologic tumor size, lymphovascular invasion, histologic tumor type, size of SLN metastases, total number of involved nodes, modified Bloom-Richardson score, adjuvant systemic therapy use, and patient age. Univariable analysis showed that only hormone receptor status, pathologic tumor size, and modified Bloom-Richardson score were associated with locoregional recurrence for the entire patient population. When the univariable models were adjusted for treatment arm, the same baseline variables remained significantly associated with locoregional recurrence-free survival. Table 4 shows univariable and multivariable (adjusted for treatment arm) analyses of prognostic factors and their association with locoregional recurrence.

As previously reported by Jagsi *et al.*[6], there were radiation protocol deviations among 335 patients in both treatment arms. Of the 335 patients, 228 had port films available for review and 107 had no radiation treatment. There were no significant differences between treatment arms in the use of protocol-prohibited nodal fields. High tangents were used in 51 percent of patients. Fifteen percent of patients received a third field treating supraclavicular nodes. There were no differences between the two treatment arms related to patient or tumor characteristics and prevalence of supraclavicular irradiation. Further analysis of the recurrence data from these 335 patients revealed that only “no radiation” was associated with an increased risk of local recurrence (P = 0.004) but not regional recurrence (P = 0.80) (Table 5).

DISCUSSION

Typical of breast cancer in the United States, most women enrolled in Z0011 were postmenopausal and had hormone-receptor positive tumors. Critics argued that the initial report with a follow-up of 6.3 years was too short a follow-up for a study with such a large proportion of women with hormone-receptor positive tumors. With nearly 10 years of median follow-up, results still show a remarkably low regional recurrence rate of 1.5 percent for SLND alone.

The observation that patients with hormone-receptor positive tumors may experience a recurrence later than those with hormone-receptor negative tumors is valid. Anderson et al.[5] examined the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program data for annual hazard rates of death from breast cancer. They found two distinct recurrence hazard rate patterns for patients with ER-negative and ER-positive tumors. The hazard rates for patients with ER-negative tumors peaked early and then declined. Hazard rates among patients with ER-positive tumors were relatively constant at 1.5 to 2.0 percent per year. In a study of the International Breast Cancer Study Group’s Trials I through V, Colleoni *et al.*[7] found that among over 4,000 patients, those with estrogen-receptor positive disease initially had lower annualized recurrence rates compared to those with estrogen-receptor negative disease. However, beyond five years, patients with ER-positive cancers had higher hazard rates.

Axillary recurrences, however, are known to occur relatively early post-surgical treatment. In NSABP B-04, the median time to axillary recurrence was 14.8 months.[4] This recurrence time was seen in patients with palpable tumors who were treated without adjuvant systemic therapy. In a study by Greco *et al.*[8] examining patients treated with breast-conserving therapy with whole breast irradiation and some use of tamoxifen, the median time to axillary recurrence was 30.6 months. Martelli *et al.*[9] performed a similar study and reported a median time to axillary recurrence of 33 months. ACOSOG Z0010 reported a median time to axillary recurrence of 19.1 months.[10, 11] In the current study, the median time to regional recurrence was 48 months.

Nearly all of the patients in ACOSOG Z0011 received adjuvant systemic therapy. Numerous studies report the continuing diminution of locoregional recurrence in breast cancer. Improvements in adjuvant systemic therapy have resulted in decreased locoregional recurrence rates. The Early Breast Cancer Trialists' Collaborative Group **(**EBCTCG) overview demonstrated that adjuvant postoperative tamoxifen decreases locoregional recurrence rates by nearly 50 percent when compared to placebo.[12] The use of aromatase inhibitors further diminishes locoregional recurrence when compared to tamoxifen.[13] Cytotoxic chemotherapy and targeted anti-HER2 therapy improve locoregional recurrence to an even greater extent.[14-16] Anti-Her2 targeted therapy has similarly contributed to the further diminution of locoregional recurrence.[17] Thus, it is not surprising that a population in which virtually all patients were treated with adjuvant systemic therapy, such as those patients in the ACOSOG Z0011 study, should experience a low locoregional recurrence rate even with 10 years of follow-up. In addition to the benefit of systemic therapy and radiotherapy on local control, in many clinically node-negative patients with Stage 1 and 2 cancers, the excised sentinel node is often the only involved node.[18-20]

The impact of off-protocol nodal irradiation on rates of regional control cannot be determined.[6] Based on the subset of 335 patients for whom detailed radiation treatment information was available, 51 percent of the patients in this study received high tangents with treatment to within 2 cm of the humeral head which may merely reflect radiation oncologist's preference. However, 15 percent of the patients were treated with a prohibited third field and 11 percent of the patients received no radiation at all. No difference was seen in patient characteristics or outcomes among those who received nodal irradiation and those who did not, and no difference in locoregional recurrence was seen by applying a prohibited third field. Jagsi *et al.* concluded: "Finally, it is critical to recognize that our observations should not be taken to suggest that the nodal radiation administered to patients in Z0011 was necessary or beneficial."

Low regional recurrence rates in Z0011 should not be surprising. Randomized studies of SLND in the past comparing ALND to no ALND show considerably fewer regional recurrences than anticipated based upon the incidence of nodal metastases in the ALND arm. Despite a recognized false negative rate of sentinel node biopsy as high as 16.7 percent in some randomized studies,[21] few women who are clinically node-negative with a tumor-free sentinel node experience axillary recurrence. In the randomized study of Veronesi *et al.*[18] which compared SLND alone to SLND + ALND in women whose SLN was tumor-free, the false negative rate for SLND was 8.8 percent. Yet the long-term regional recurrence

rate for patients treated without axillary dissection was only 0.8 percent. NSABP B-32, a similarly designed study, showed 9.8 percent of patients in the ALND group had a false negative SLN, but only 0.5 percent of patients in the SLND-only group developed regional recurrences by eight years.[19] Houvenaeghel *et al*.[22] reported that 14,095 patients who underwent surgery for clinically N0 previously untreated breast cancer and who had sentinel node biopsy experienced a 0.51 percent axillary recurrence rate with a median time to onset of 43 months.

There is, of course, limited data for patients with tumor-involved SLN treated with SLND alone. However, there are large retrospective studies examining regional recurrence. In the largest retrospective review from the National Cancer Database (NCDB), Bilimoria *et al*.[23] found that the regional recurrence rate for patients with positive SLN who did not have ALND was only 0.4 percent for patients with SLN micrometastases and 1.0 percent for those with macrometastases. The International Breast Cancer Study Group's randomized trial IBCSG 23-01 found 13 percent of patients had additional positive nodes with ALND after SLND revealed micrometastasis.[3] Yet in the group that received SLND without ALND, only about 1 percent experienced a nodal recurrence, less than one tenth of the anticipated rate. In ACOSOG Z0011, the 27 percent occurrence of positive nodes in axillary dissection was not reflected in nodal recurrence rates among those patients who did not receive ALND.

The finding that axillary lymph nodes with metastases do not require resection is disturbing to surgeons. However, the history of breast cancer management has revealed that our preconceptions concerning the extent of operation necessary to achieve cure for patients with early breast cancer have often been excessive. Now it appears that even with long-term follow-up, selected patients with early SLN metastases do not require ALND when treated with optimal contemporary management. Locoregional control can be achieved with excellent long-term results with SLND alone, whole breast irradiation, and adjuvant systemic therapy.

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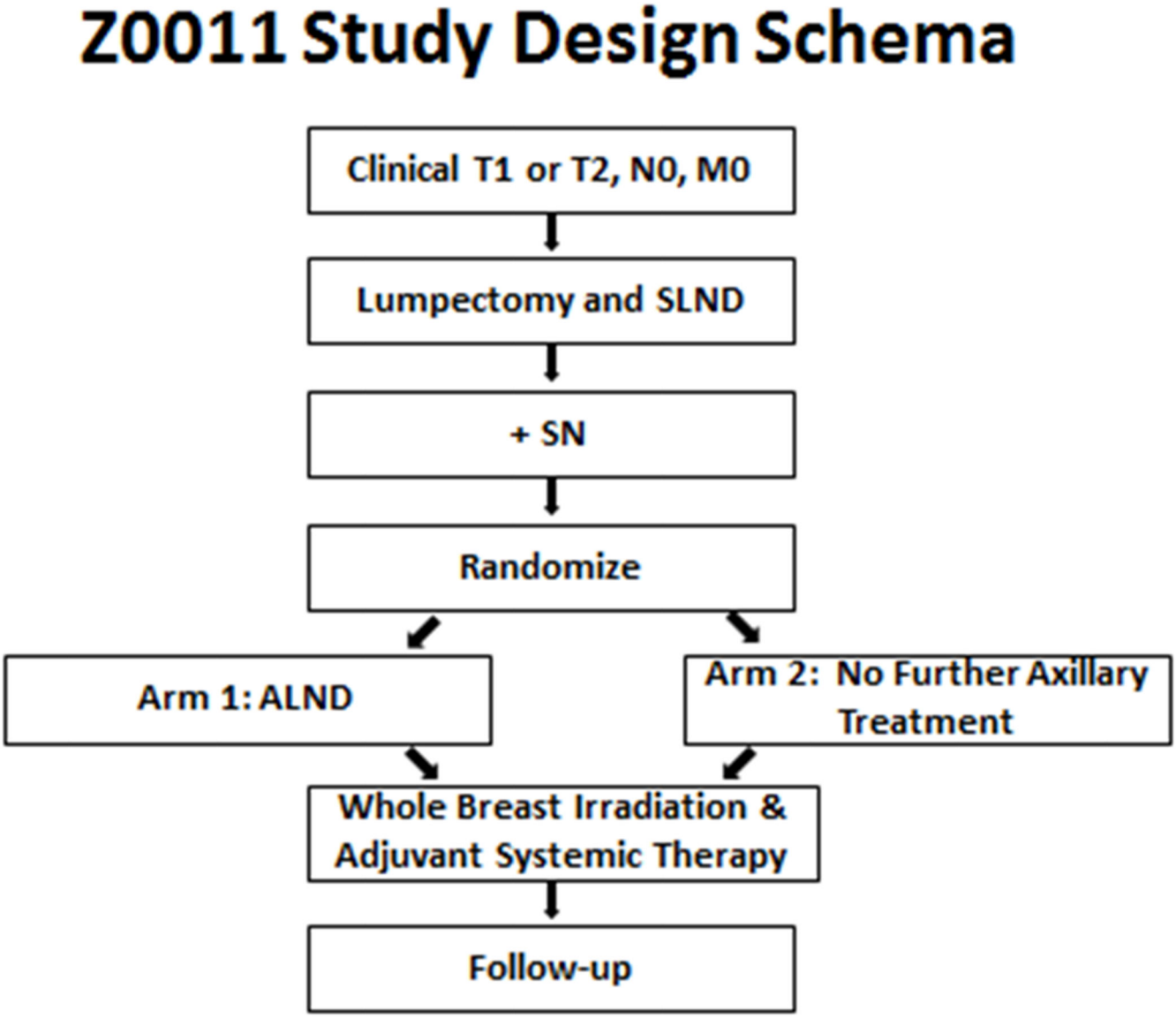

Figure 1.
Z0011 Study Design Schema

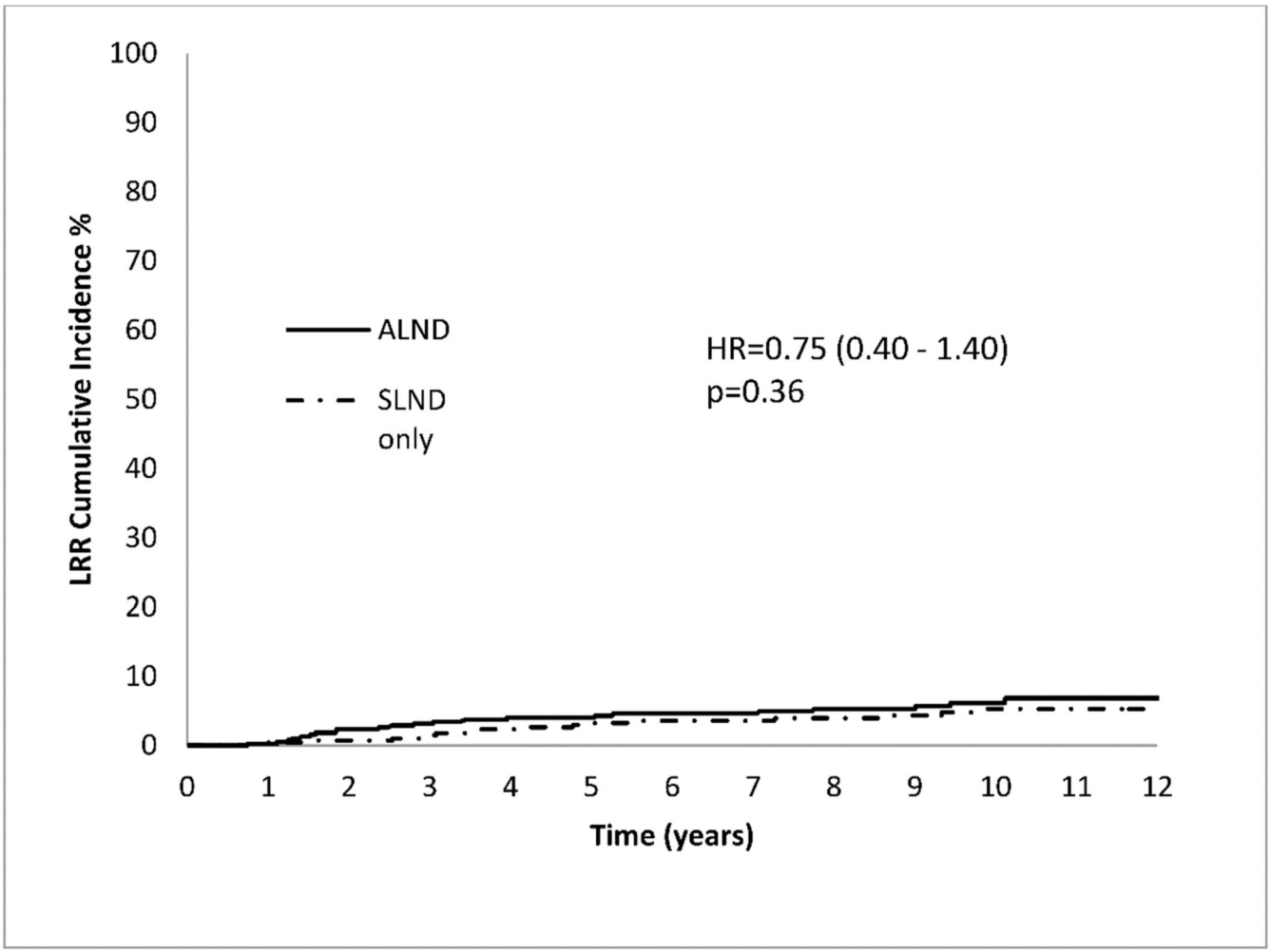

Figure 2.
Cumulative Incidence of Locoregional Recurrence by Treatment Arm

Table 1

Characteristics of Patients and Primary Tumors in the 2 Study Arms

	Intent to Treat Sample		Treatment Received Sample	
	ALND arm	SLND only arm	ALND	SLND only
	N = 420	N = 436	N = 388	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. (%)	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)

Table 2

Number and Extent of Disease of Lymph Nodes by Treatment Arm

	ALND (N = 420)	SLND only (N = 436)	*P*
Total number of nodes removed			<0.001
median	17	2	
IQR*	13,22	1,4	
Number of positive nodes			<0.001
median	1	1	
IQR*	1,2	1,1	
Number of positive nodes, no. (%)			<0.001
1	199 (58.0)	295 (71.1)	
2	68 (19.8)	76 (18.3)	
≥ 3	72 (21.0)	15 (3.6)	
Size of SN Mets, no. (%)			0.05
Micro	137 (37.5)	164 (44.8)	
Macro	228 (62.5)	202 (55.2)	

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

Table 3

Number and Cumulative Incidence of Locoregional Recurrences (%) at Specific Time Points

	ALND				SLND only			
Time	**# at risk**	**LRR events**	**Local events**	**Regional events**	**# at risk**	**LRR events**	**Local events**	**Regional events**
1 year	375	1 (0.3%)	1 (0.3%)	0 (0.0%)	394	2 (0.5%)	1 (0.2%)	1 (0.2%)
2 year	342	9 (2.4%)	8 (2.1%)	1 (0.3%)	365	3 (0.7%)	1 (0.2%)	2 (0.5%)
5 year	286	15 (4.0%)	13 (3.5%)	2 (0.5%)	279	12 (3.3%)	8 (2.2%)	4 (1.1%)
10 year	130	21 (6.2%)	19 (5.6%)	2 (0.5%)	139	17 (5.3%)	12 (3.8%)	5 (1.5%)

Table 4

Univariable and Multivariable Analyses of Predictors of Locoregional Failure

		Univariable p	*HR (CI) (univariable)*	*Multivariable p (adjusted for treatment arm only)*	*HR (CI) (adjusted for treatment arm only)*
Hormone Receptor Status					
	*Negative**	*0.002*	*1.00 (ref)*	*0.002*	*1.00 (ref)*
	Positive		*0.30 (0.14 – 0.64)*		*0.30 (0.14 – 0.63)*
Pathologic Tumor Size					
	Path tum size	*0.009*	*1.19 (1.04 – 1.36)*	*0.009*	*1.20 (1.05 – 1.37)*
Lymphovascular Invasion					
	Yes	*0.19*	*1.00 (ref)*	*0.21*	*1.00 (ref)*
	No		*0.61 (0.29 – 1.28)*		*0.62 (0.30 – 1.30)*
Histologic Type					
	Ductal	*0.88*	*1.00 (ref)*	*0.88*	*1.00 (ref)*
	Lobular		---		---
	Both		---		---
	Neither		*0.43 (0.06 – 3.16)*		*0.43 (0.06 – 3.16)*
Sentinel Node Met Size					
	Micro	*0.16*	*1.00 (ref)*	*0.13*	*1.00 (ref)*
	Macro		*0.62 (0.32 – 1.20)*		*0.60 (0.31 – 1.16)*
# Positive Total LN					
	0	*0.92*	*1.00 (ref)*	*0.85*	*1.00 (ref)*
	1		*1.21 (0.16 – 8.94)*		*1.08 (0.14 – 8.11)*
	2		*1.12 (0.14 – 9.09)*		*0.98 (0.12 – 8.15)*
	3 or more		*0.80 (0.08 – 7.67)*		*0.63 (0.06 – 6.35)*
Modified Bloom-Richardson Score					
	I	*0.001*	*1.00 (ref)*	*0.001*	*1.00 (ref)*

Table 5

Recurrence Rates for Patients with Known Radiation Protocol Deviations

		Total patients	LOCAL		REGIONAL		TOTAL LRR	
			# events (10 yr CI)	p	# events (10 yr CI)	p	# events (10 yr CI)	p
WBI done (from CRF)								
	Yes	540	16 (3.3%)	0.002	5 (1.0%)	---	21 (4.3%)	0.002
	No	65	6 (12.2%)		0 (0.0%)		6 (12.2%)	
RT done (355 pts with extra info)								
	Yes	228	4 (1.9%)	0.004	4 (1.9%)	0.80	8 (3.8%)	0.015
	No	107	8 (9.1%)		1 (1.1%)		9 (10.2%)	
High Tangents (228 pts with extra info)								
	Yes	73	3 (4.3%)	0.64	1 (1.4%)	0.82	4 (5.8%)	0.59
	No	69	1 (1.5%)		1 (1.6%)		2 (3.0%)	
	N/A or Unknown	86	0 (0.0%)		2 (2.8%)		2 (2.8%)	
Supraclavicular (228 pts with extra info)								
	Yes	43	0 (0.0%)	---	0 (0.0%)	---	0 (0.0%)	---
	No	185	4 (2.3%)		4 (2.3%)		8 (4.6%)	