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Expanding Implementation of ACOSOG Z0011 in Surgeon Practice

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Abstract

Background and Objectives—After publication of ACOSOG Z0011, surgeons at our institution limited axillary surgery to sentinel lymph node dissection (SLND) in 76% of patients meeting trial eligibility criteria. Our study objective was to assess incorporation of the trial data into practice 5 years later.

Patients and Methods—Patients with clinical T1–2, N0 invasive breast cancer undergoing breast conserving surgery were included. Comparisons were made between patients who underwent axillary lymph node dissection (ALND) to those that had no further surgery.

Results—A total of 396 patients were included. Twelve percent (48/396) had positive SLNs; ALND was performed in 8% (4/48). Patients who underwent ALND were more likely to have 2 positive SLNs (50%, 2/4 vs. 2%, 1/44, $p=0.02$) and microscopic extranodal extension (75%, 3/4 vs. 18%, 8/44, $p=0.03$) than those that did not undergo ALND. Patients who underwent ALND also had a higher nomogram-predicted probability of having additional positive non-SLNs (53%) than those who had SLND alone (22%) ($p=0.0002$). No patients had intra-operative assessment of SLNs performed.

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Conflicts of Interest

There are no conflicts of interest to disclose

Conclusions—The practice of omitting ALND in ACOSOG Z0011 eligible patients has expanded over 5 years. Clinicopathologic features continue to impact this decision. Intra-operative SLN assessment is no longer performed.

Introduction

Historically, axillary lymph node dissection (ALND) was performed for breast cancer patients with both node-positive and node-negative disease. The introduction of sentinel lymph node dissection (SLND) allowed for a minimally invasive alternative for nodal staging with less morbidity, improved patient-reported outcomes,¹ and equivalent oncologic outcomes.^{2–5} Randomized trials confirmed that there was no benefit to completion ALND for patients with pathologically negative sentinel lymph nodes (SLN).^{3, 4} For those with a positive SLN, ALND remained the standard approach when SLNs were involved with metastatic disease. The need for extensive nodal surgery when only small volume metastases were identified was questioned leading to the conduct of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial.

ACOSOG Z0011 was a prospective, randomized trial designed to evaluate the impact of ALND on locoregional recurrence and overall survival in patients with early stage breast cancer and positive SLNs. It enrolled patients with clinical T1–2, N0, M0 breast cancer treated with breast conserving surgery (BCS) that were found to have 1–2 positive SLN on standard pathologic evaluation. Patients were randomized to undergo ALND or SLND alone. In the initial report of the study results there were no differences in locoregional recurrence or overall survival at a median follow-up of 6.4 years.^{6, 7} The investigators concluded that routine use of ALND was not justified and that it may safely be omitted in selected patients who met the trial eligibility criteria. This data has recently been updated to give 10 year follow-up data with continued equivalency between the groups' locoregional recurrence (6.2% ALND vs 5.3% SLND alone, $p=0.36$)⁸ and overall survival (83.6% ALND vs 86.3% for SLND, $p = 0.40$).⁹

NCCN guidelines cite these data in support of their recommendation for omission of ALND in Z0011 eligible patients,¹⁰ and in fact, omission of ALND in appropriate patients is considered a quality metric for breast surgery.¹¹ A review of the National Cancer Database reported on >74,000 patients who met Z0011 criteria with 1–2 positive nodes. The proportion of patients undergoing ALND dropped from 94% in 1998 to 77% in 2009 (the year before trial publication) to 44% in 2011 after release of the results ($p<.001$).¹² Other studies have shown a decrease in ALND as the trial results have been incorporated into clinical guidelines.¹³

After the initial trial results were published, we conducted a multidisciplinary conference at our institution that included surgeons, medical oncologists, radiation oncologists, and pathologists to discuss our group plans for implementing the data into practice. As a group, we formulated general guidelines for incorporation of the data based on the eligibility criteria of the trial.¹⁴ This discussion stressed the need for adherence to the Z0011 criteria for consideration of omission of ALND, however, we acknowledged that some groups may have been underrepresented in the ACOSOG Z0011 trial, such as those with ER negative

disease, young age, or lobular histology. In these groups, we recommend consideration of all clinicopathologic features as well as discussion with multidisciplinary colleagues in deciding whether to omit ALND. The use of nomograms to predict additional positive non-SLNs can be especially helpful in these situations. A year after this conference, we evaluated our practice patterns before and after the trial. We found that 85% (53/62) of SLN positive patients that otherwise met the Z0011 eligibility criteria underwent ALND before the Z0011 trial results were published, compared to 24% (10/42) after publication ($p<0.001$). Since completion ALND was no longer routinely performed, surgeons at our institution reduced their use of intra-operative pathologic assessment of SLN from 69% before the trial to 26% after the trial ($p<0.001$) reducing operative times and costs for all patients, regardless of SLN result.¹⁵ The goal of this study was to evaluate our practice 5 years after the publication of ACOSOG Z0011 trial results.

Patients and Methods

A review of consecutively treated patients with clinical T1–2, N0 breast cancer undergoing BCS and SLND during the 12-month period of September 1, 2015 to August 31, 2016 (5 years after our previously reported cohort) was performed.¹⁵ Twenty-three breast surgical oncologists operated during this time. Patients who had neoadjuvant chemotherapy, neoadjuvant endocrine therapy, converted to mastectomy, had ≥ 3 positive SLN, or tumors >5 cm on final surgical pathology were excluded. At diagnosis, all patients underwent evaluation with physical examination, mammography, and ultrasound of the breast and draining nodal basins per our institutional protocol. Lymph nodes with abnormal appearance on ultrasound underwent fine needle aspiration biopsy (FNAB).¹⁶ Patients with an ultrasound that did not show any suspicious lymph nodes, or those with a suspicious US but negative FNAB, were considered clinically node negative and included in this analysis. Patients with FNAB showing nodal metastasis were considered clinically node positive and excluded. Data was collected from review of electronic medical records including radiology, operative, and pathology reports as well as clinic notes. Only patients who received their complete course of radiation at our institution were included in analysis of radiation practice. In node positive patients, clinicopathologic data was used to calculate the percent risk of having additional non-SLN involvement using a previously developed nomogram.¹⁷

Comparisons between groups were made using Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables as appropriate. P values shown are based on two-sided comparison with a significance level of 0.05. (SAS Enterprise Guide 5.1, Cary NC). This study was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board.

Results

A total of 396 patients were included in the analysis. No patient had intraoperative assessment of their SLN performed. SLN were positive in 48 (12%) and negative in 348 (88%) patients (Figure 1). Node positive patients were younger than the node negative patients (median 58.5 vs. 63 yrs., $p=0.03$). There were no significant differences between node positive and node negative patients with respect to menopausal status, clinical tumor

size, tumor histology, grade, or receptor status. Significant differences were seen in surgical pathology between the groups (Table 1). Node positive patients had larger pathologic tumor sizes (1.9 vs 1.4 cm, $p<0.0001$) and were more likely to have lymphovascular invasion on surgical pathology (27.1% vs. 6.9%, $p<0.0001$). The median number of nodes removed was 2 in both SLN-positive and negative groups.

Node Positive Patients

Of the 48 patients with a positive SLN, 4 (8%) underwent ALND. The mean number of nodes removed at their first operation was similar between the groups (2.5, $p=1$). Patients who underwent ALND were more likely to have 2 positive SLNs (50%, 2/4) than those who did not undergo ALND (2%, 1/44) ($p=0.02$). The ALND group also had a higher proportion of nodal metastases with microscopic extranodal extension (75%, 3/4) than the non-ALND group (18%, 8/44) ($p=0.03$). There were no differences between groups with regards to size of nodal metastasis, or the proportion of patients with micrometastasis. There were two patients with lobular histology, one underwent ALND, the other SLND alone. Patients who underwent ALND had a higher predicted probability of having additional positive non-SLNs by a published nomogram¹⁷ (53%) than those that did not have ALND (22%) ($p=0.0002$). One patient (25%) in the ALND group had additional positive non-SLNs. This patient had a tumor with lobular histology, and 2/2 SLNs with metastatic disease with the largest focus measuring 0.7 cm. Using our published nomogram, the predicted probability of additional positive disease was 70%.¹⁷ These results are summarized in Table 2.

Adjuvant Therapy

Node positive patients were more likely to receive adjuvant chemotherapy (66.7% vs 24.6%, $p < 0.001$). Endocrine therapy was used in 92.4% (293/317) of the hormone receptor (HR)-positive, node negative patients and 97.8% (44/45) of the node positive patients who were HR-positive.

A total of 376/396 (94.9%), patients received radiation therapy following their segmental mastectomy. All patients who did not receive radiation therapy were node negative. There was one patient (56 years old) who refused radiation. Excluding this patient, the mean age of those who did not receive radiation was 74.5 years (range 68–88). Of those receiving radiation, 292 received their complete course at our institution. Of these, 264 were node negative and 28 were node positive. Of the 264 node negative patients, 39 (14.8%) received partial breast irradiation (2 brachytherapy, 27 proton therapy, 10 electron based partial breast), the other 225 (85.2%) received whole breast irradiation. All 28 of the node positive patients received whole breast irradiation. Radiation fields were designed to cover the low axilla in 92.9% (26/28) with 39.3% (11/28) receiving comprehensive regional nodal irradiation.^{14, 18} Only 1 patient who underwent ALND received radiation at our institution so differences in radiation fields between patients that underwent ALND and those that underwent SLND alone could not be evaluated.

Discussion

The current study indicates that surgeons at our institution have increased their incorporation of the ACOSOG Z0011 trial data into their practice since our initial report published one year after the trial data became available (Table 3). Specifically, in that first year after publication of the trial data, completion ALND was performed in 24% of patients meeting Z0011 criteria versus in 8% in the current cohort. In addition, the use intraoperative assessment of the SLND was seen in 26% of patients in the first year after publication of the trial data but has been completely abandoned in our current practice. These data suggest that surgeons at our institution have become more comfortable with this approach.

The ACOSOG Z0011 trial represented a significant advance in the treatment of breast cancer patients. As with any trial, incorporation into practice is a complex process that can vary with time, with reports of a 17-year lag between publication of trial results and trial adoption in some cases.^{19, 20} A survey of the American Society of Breast Surgeons conducted in 2011 showed that 97% were familiar with the trial, while only 56.9% reported implementation into their practice.²¹ Similarly, a review of the NCDB showed completion ALND was omitted in 56% of eligible patients in 2011.¹² In our institution, 76% of SLN-positive patients omitted ALND in 2011 – while higher than these national figures, this still implies reservations regarding implementation of the data.^{15, 22} The current proportion of 8% demonstrates increasing acceptance of this approach, but also shows that there is personalization to surgical management of the axilla in these patients. There is no data to demonstrate the national rate of trial incorporation to compare the rapidity of incorporation at our institution compared to national practice patterns. However, we hypothesize that open multidisciplinary communication concerning the trial and its application in specific patients contributed to increasing acceptance.

Compared to patients who did not undergo ALND, patients who underwent ALND had a higher predicted probability of having additional positive non-SLNs by a published nomogram that incorporates multiple pathologic features (53% vs. 22%).¹⁷ It is important to note that the nomogram scores were calculated for the purposes of this study and it is not known whether the individual surgeon calculated this risk and figured it into their clinical decision making process. Patients who underwent ALND were also more likely to have 2 positive SLNs instead of a single positive node (50% vs. 2%) and evidence of extranodal extension (75% vs. 18%). In our previous study, 75% (n = 3/4) of node-positive patients with lobular tumors underwent ALND.¹⁵ With only 2 patients in the current study having lobular tumors, we cannot comment as to whether this histology is continuing to impact the surgeon's decision regarding recommending completion ALND. Similarly, though the sample size is too small to draw a conclusion, ALND was omitted in patients in this study who had HER2 positive and triple negative disease.

Minimizing axillary surgery has significant benefits related to surgical morbidity. The NSABP B-32 trial, which randomized SLN-negative patients to ALND versus no further surgery, showed equivalent oncologic outcomes however the SLNB-only group had lower rates of shoulder abduction deficit, arm volume difference, and paresthesia than ALND.²³ Quality of life, arm and breast symptoms, and work and social activity restrictions were all

improved by SLNB alone.¹ These findings were also seen in the Z0011 trial as the SLND cohort had fewer wound infections (3% vs 8%, $p=0.0016$), seromas (6% vs. 14%, $p=0.0001$), and reports of paresthesia (9% vs. 39%, $p<0.0001$). The primary morbidity of concern in most breast cancer patients is lymphedema, which was also lower in the SLND cohort (2% vs. 13%, $p<0.0001$).²⁴

An important finding in this study is that no intraoperative assessments of SLN were performed. This is compared to 26% of cases in 2011, and 69% in 2010.¹⁵ In our previous report, the use of frozen section dropped from 55% in the first 6 months to 22% in the last 6 months. Several groups have reported on the decreased use of SLN frozen section after Z0011,^{25, 26} which decreases operative time and provides cost savings.^{15, 25, 27} Fillion et al. showed that eliminating intra-operative assessment decreases the cost of SLND from \$4319 to \$2036, with a further 20% cost reduction per patient in which ALND was avoided.²⁷ Given these observations and the lack of oncologic benefit to additional axillary surgery, the American Society of Breast Surgeons included omission of ALND in appropriate SLN-positive patients in their *Choosing Wisely*® Campaign.¹¹

One of the limitations of this study is inability to assess the impact of surgical practice change on other adjuvant therapies given the small sample size of patients who completed their care at our institution. However, 92.9% of the node positive patients had coverage of the low axilla suggesting an impact on radiation planning. The complexity of changing cancer care paradigms also hinders our ability to differentiate adjuvant treatment changes attributable to surgical practice, in contrast to emerging data in those fields.^{28–30} It should also be noted that all patient in this study underwent preoperative nodal assessment with ultrasound and biopsy of abnormal nodes. While the use of nodal ultrasound in patients with early stage breast cancer is controversial, we feel that it provides valuable information in determining the optimal therapy for patients. We have previously reported that patients with nodal disease identified on ultrasound, even if 2 suspicious nodes were seen, were more likely to have 3 positive nodes at surgery than patients whose nodal disease was identified.³¹ Similar results have been reported from Moffitt Cancer Center and the Mayo Clinic.^{32, 33} Lastly, the retrospective nature of this review does not allow for complete understanding of which factors prompted surgeons to recommend further surgery. However, review of notes detailing preoperative discussion reflected multifactorial rationale in all cases where ALND was performed. Specific concerns cited included age <40 years old, extent of extranodal extension, number of positive nodes, size of nodal metastasis, and the probability of additional disease predicted by nomograms.

Conclusion

The current study indicates that surgeons at our institution have become increasingly comfortable with the Z0011 trial data after 5 years. The proportion of SLN-positive patients who underwent ALND dropped to 8% and the use of intra-operative SLN assessment has been abandoned. This shows an acceptance of the trial data. Although the numbers of patients are too small to draw definitive conclusions, it appears that surgeons continue to personalize their recommendations.

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Clinical Practice Points

ACOSOG Z0011 evaluated breast cancer patients with clinical T1–2, N0, M0 disease undergoing breast conservation surgery who were found to have 1 or 2 positive sentinel nodes. The trial randomized patients to axillary lymph node dissection versus no further axillary surgery and found equivalent locoregional and survival outcomes. The investigators concluded that routine use of ALND was not justified and that it may safely be omitted in selected patients who met the trial eligibility criteria. This data has recently been updated to give 10-year follow-up data with continued equivalency in outcomes. After publication of this trial, we surveyed surgeon practice patterns in our institution in the year before and the year after the trial and found a change in practice patterns. The goal of this study was to see if these changes expanded over the next 5 years.

In this study, 396 patients with clinical T1–2, N0, M0 breast cancer underwent breast conserving therapy with sentinel lymph node dissection. In the 48 patients who were found to have a positive sentinel node, only 8% underwent axillary lymph node dissection. This compares to 24% in the year immediately after the trial publication suggesting that surgeons have become more comfortable with this data and its implementation into practice. The use of intra-operative frozen section analysis of sentinel nodes has been abandoned. The implementation of ACOSOG Z0011 findings is standard, but personalization of axillary management is still reasonable.

Figure 1.
Flow diagram of the patient cohort's pathologic lymph node findings and surgical axillary management.

Table 1

Clinicopathologic Features of Node Positive and Negative Patients

		Node Positive N=48	Node Negative N=348	P Value
Median Age		58.5 (29–82)	63 (33–88)	0.03
Menopausal Status:	Pre	13 (27.1%)	64 (18.6%)	0.17
	Post	35 (72.9%)	280 (81.4%)	
	Unknown		4	
Clinical Tumor Size (cm)		1.87 cm (0.6–5)	1.54 cm (0.2–5)	0.02
Clinical T Stage:	T1	33 (68.8%)	279 (80.2%)	0.07
	T2	15 (31.3%)	69 (19.8%)	
Tumor Histology:	Ductal	45 (93.8%)	304 (87.4%)	0.50
	Lobular	2 (4.2%)	37 (10.6%)	
	Mixed	1 (2.1%)	5 (1.4%)	
	Other	0	2 (0.6%)	
Nuclear Grade:	1	12 (25%)	116 (33.5%)	0.45
	2	27 (56.3%)	165 (47.7%)	
	3	9 (18.8%)	65 (18.8%)	
	Missing		2	
Tumor Subtype:	HR ^I ₊ /HER2 [−]	42 (87.5%)	292 (83.9%)	0.92
	HR ⁺ /HER2 ⁺	3 (6.3%)	25 (7.2%)	
	HR [−] /HER2 ⁺	1 (2.1%)	9 (2.6%)	
	HR [−] /HER2 [−]	2 (4.2%)	22 (6.3%)	
Intra-Op SLN Assessment		0	0	
SLN Removed:	1	17 (35.4%)	122 (35.1%)	0.23
	2	13 (27.1%)	98 (28.2%)	
	3	9 (18.8%)	68 (19.5%)	
	>3	9 (18.8%)	60 (17.2%)	
Median number of nodes removed at first operation		2	2	0.9
Pathologic Tumor Size		1.91 (0.13–4.5)	1.37 (0.05–4.8)	<.0001
Pathologic T Stage:	T1	28 (58.3%)	288 (82.8%)	<.0001
	T2	20 (41.7%)	60 (17.2%)	
Lymphovascular Invasion Present		13 (27.1%)	24 (6.9%)	<.0001
Adjuvant Chemotherapy:	Yes	32 (66.7%)	80 (24.6%)	<.0001
	No	16 (33.3%)	245 (75.4%)	
	Unknown	0	23	

		Node Positive N=48	Node Negative N=348	P Value
Hormonal therapy:	Yes	44 (91.7%)	293 (84.2%)	0.24
	No	4 (8.3%)	50 (14.4%)	
	Unknown		5 (1.4%)	
Radiation therapy:	Yes	48 (100%)	328 (95.6%)	0.23
	No		15 (4.4%)	
	Unknown		5	

¹_{HR}= Hormone Receptor

Table 2

Comparison of node positive patients who underwent sentinel lymph node dissection alone versus those that underwent completion axillary node dissection

		No ALND N=44	ALND N=4	P Value
Median Age		59.5 (29–82)	48 (38–76)	0.37
Menopausal Status:	Pre	11 (25%)	2 (50%)	0.29
	Post	33 (75%)	2 (50%)	
Clinical Tumor Size (cm)		1.90 (0.6–5)	1.6 (1.5–1.8)	0.05
Clinical T Stage:	T1	29 (65.9%)	4 (100%)	0.29
	T2	15 (34.1%)		
Tumor Histology:	Ductal	42 (95.5%)	3 (75%)	0.09
	Lobular	1 (2.3%)	1 (25%)	
	Mixed	1 (2.3%)		
Nuclear Grade:	1	12 (27.3%)	0	0.48
	2	24 (54.6%)	3 (75%)	
	3	8 (18.2%)	1 (25%)	
Tumor Subtype:	HR+/Her2–	38 (90.5%)	4 (100%)	0.89
	HR+/HER2+	3 (6.8%)		
	HR–/HER2+	1 (2.3%)		
	HR–/HER2–	2 (4.6%)		
Pathologic Tumor Size		1.91 (0.13–4.5)	1.90 (1.5–2.5)	0.98
Pathologic T Stage:	T1	25 (56.8%)	3 (75%)	0.48
	T2	19 (41.2%)	1 (25%)	
Lymphovascular Invasion Present		11 (25%)	2 (50%)	0.29
Number of Nodes removed at first operation:				
	1	16 (36.4%)	1 (25%)	0.29
	2	9 (20.5%)	0	
	3	9 (20.5%)	3 (75%)	
	>4	10 (22.7%)	0	
	Median	2	3	
Number Positive SLN:	1	43 (97.7%)	2 (50%)	0.02
	2	1 (2.3%)	2 (50%)	
Size of SLN Metastasis (mm)		4.33 (0.3–13)	5.8 (0.5–9)	0.38
SLN Micrometastasis:		12 (27.9%)	1 (25%)	0.9
Extranodal Extension Present		8 (18.2%)	3 (75%)	0.03

		No ALND N=44	ALND N=4	P Value
Nomogram prediction of additional positive non-SLN ¹⁷		22% (range 1–57)	53% (range 37–70)	.0002
Adjuvant Chemotherapy:	Yes	29 (64.9%)	3 (75%)	0.71
	No	15 (34.1%)	1 (25%)	
Hormonal therapy:	Yes	40 (90.9%)	4 (100%)	0.53
	No	4 (9.1%)	0	
Radiation therapy:	Yes	44 (100%)	4 (100%)	1.0

Table 3

Implementation of ACOSOG Z0011 Results into Practice

	Before Publication April 2009–March 2010¹⁵	Immediately After Publication Sept 2010–Aug 2011¹⁵	5 Years Later Sept 2015–Aug 2016	P Value
ALND in SLN Positive patients	85%	24%	8%	<.0001
Use of Intra-operative assessment	69%	26%	0%	<.0001