

## RESEARCH ARTICLE

# Managing the Axilla in Early Breast Cancer. Impact of ACOSOG Z0011 Trial in Changing Practices in a Low Middle Income Country

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### Abstract

**Objective:** To determine the impact of the trial on surgeon practice patterns at our institution. **Methodology:** A comparison of patients undergoing surgery for early breast cancer before and after the implementation of the new guidelines was done. We adopted the new guidelines in April 2015. Patients meeting Z0011 inclusion criteria were identified. For group A (Pre Z0011) patients operated between Jan to Dec 2013 were studied. And for Group B (Post Z0011) patients operated between July 2014 to Jun 2015 were included. Clinicopathologic data were compared between the two groups. **Results:** There were 318 patients with clinical T1-2 tumors planned for breast conservation. 68% patients had T1 tumor and 32% had T2. 92% of the patients had IDCa. There were 150 patients in the pre-Z0011 group and 168 post-Z0011. 68% of the patients in Group A were ER+ve while 70% in group B. 38 (25.7 %) patients were sentinel lymph node (SLN) positive in the pre-Z0011 group versus 34 (21 %) post-Z0011 ( $p = 0.392$ ). Before Z0011 100 % (38/38) of SLN-positive patients underwent axillary node dissection (ALND) versus 17 % (6/34) after Z0011 ( $p < 0.01$ ). Median no of SLNs identified in group A were 1.3 and group B were 1.4. There was a decrease in median operative times of the two groups (80 vs. 60 min,  $p < 0.01$ ). There was a significant decrease in the overall hospital stay of sentinel lymph node positive patients in between the two groups (2.1 days vs 1.3 days  $p$  value  $< 0.01$ ). **Conclusions:** Implementation of Z0011 guidelines has resulted in significant short term advantages in terms of reduced axillary dissections, shorter operative times and shorter hospital stays.

**Keywords:** Z0011- Breast cancer- axillary dissection- sentinel lymph node

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### Introduction

A complete axillary node dissection for patients with breast cancer was introduced in the 1800s, both for staging and to achieve regional disease control (Halsted 1894; Cotlar et al., 2003). Axillary surgery however is associated with an increased risk of adverse outcomes, including lymphedema (14%), limited shoulder/ arm motion (28%), and neuropathic pain (31%). A desire to minimize morbidity led to the development of the sentinel lymph node (SLN) biopsy technique. With the introduction and validation of SLN biopsy, complete axillary node dissection as the initial axillary intervention is no longer an acceptable option for patients in the United States who have no palpable or ultrasound evidence of axillary metastases (Krag et al., 2010; Fleissig et al., 2006).

Prior to 2011, sentinel lymph node (SLN) biopsy was currently the standard of care for staging the clinically negative axilla in breast cancer patients, with axillary lymph node dissection (ALND) reserved for patients with

clinical axillary metastases or metastases found on SLN biopsy (Carlson et al., 2000; Bevers et al., 2009). However, this treatment paradigm has changed based on the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 randomized trial initially reported in 2010 (Giuliano et al., 2010) and again reported in 2011 (Giuliano et al., 2011). This trial included patients with clinically node negative invasive breast cancer treated with lumpectomy and whole breast radiation. Patients with 1 or 2 positive SLNs were randomized to undergo completion ALND or observation. In this select group of patients, no significant difference in survival or locoregional recurrence was observed between the patients undergoing SLN biopsy alone and those who received a completion ALND. The ACOSOG Z0011 study has been heralded by many as a “practice changing trial”, (Morrow and Giuliano 2011; Caudle et al., 2011). Altering the treatment paradigm for axillary metastases and sparing eligible women the morbidity of a completion ALND without sacrificing survival or local control. However, others have argued

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that the stringent inclusion criteria associated with the trial limits the true clinical significance of these findings, as a relatively small proportion of patients will be eligible (Guth et al., 2012).

We at Shaukat Khanum Memorial Cancer Hospital and Research Center adopted the Z0011 guidelines since 2014. All patients who fit into the Z0011 criteria undergo lumpectomy and sentinel lymph node biopsy to assess the axilla. Only patients who had 3 or more positive lymph nodes on Sentinel biopsy underwent a completion axillary dissection. All other patients with a positive sentinel lymph node were offered post op radiotherapy.

We did a year on year comparison before and after the implementation of Z0011 guidelines. The objective of the study was to compare the effect of Z0011 guidelines on changing surgical practices at Shaukat Khanum Hospital.

## Materials and Methods

### Methodology

All patients presenting at Shaukat Khanum hospital with clinical T1-2N0M0 invasive breast cancer who underwent breast conservation therapy (BCT) and SLND were included in the study. Patients were divided into two groups. Group A (Pre Z0011 Group) consisted of patients before the implementation of Z0011 guidelines from 01/01/2013 to 31/12/2013. Group B (Post Z0011 group) consisted of patients after implementation of guidelines from 01/07/2014 to 30/06/2015. Patient demographics, Tumor size, Type, ER/PR status, no. of sentinel lymph nodes identified and no of ALNDs performed were recorded. Total operative time and Length of hospital stay were also recorded.

Patients who had neoadjuvant chemotherapy and patients with tumors > 5 cm were excluded. All patients in both cohorts were initially staged based on physical examination, mammography, breast and nodal ultrasound, and pathological assessment of biopsies. Positive SLN were defined as metastasis seen on standard H and E staining. Data were collected from review of electronic medical records, including clinical, pathological, and radiologic reports, as well as operative logs. Comparisons were made between groups using chi square test for categorical variables and the Mann-Whitney test or logistic regression for continuous variables as appropriate. P values shown are two-sided values. This study was approved by the Institutional Review Board.

## Results

A total of 310 patients were included in the study. 148 patients in Pre Z0011 group and 162 patients in Post Z0011 group. Both the groups were similar in terms of age, menopausal status, tumor type, tumor stage, receptor status and grade. Comparison between both the groups can be seen in Table 1.

During surgery 25.7% patients in group A and 21% patients in Group B had positive sentinel lymph nodes. Median number of lymph nodes were similar in both the groups (2.0 vs 2.3 p value 0.789). All the patients in Group A underwent a completion ALND where as only 3.7%

Table 1. Demographic Comparison of Both the Groups

	PRE Z0011	POST Z0011	P value
No. of patients	148	162	0.896
Age	51	49	0.767
Premenopausal	70 (47.3%)	85(52.5%)	0.476
Postmenopausal	78 (52.7%)	77(47.5%)	0.475
Stage T1	55	59.6	0.345
Stage T2	45	40.4	0.455
Median Tumor Size	20.0 mm	19.0 mm	0.875
IDCa	86.5	88.9	0.665
ILCa	5.4	3.1	0.546
Other	8.1	8	0.876
ER+	72.3	75.9	0.485
PR+	63.5	60.5	0.658
H2N	22	22.4	0.458
DCIS	34.5	42.5	0.089
Grade			
1	2.1	2	0.524
2	49.3	42.5	0.446
3	48.6	55.6	0.687

patients in group B underwent a completion ALND. There was a 22% reduction in the number of ALNDs performed (25.7 vs. 3.7%, p value <0.001). Median number of lymph nodes removed during completion ALND in group A were 19 and in group B were 15 (p value 0.454). When overall comparison is made for all the patients undergoing surgery the median number of lymph nodes were 6 in group A versus 2 in group B (p value <0.001).

When analyzed for possible reasons for undergoing completion ALND, Post Z0011 surgeons were more likely to perform ALND if more SLNs were identified (1 vs 3 p value 0.004). Tumor type, size and receptor status had no effect on whether ALND would be performed or not. Median operating time for Group A was 80min and for Group B was 60 min (p value 0.003). Length of hospital stay was 2.1 for group A and 1.3 for group B (p value <0.001).

Comparison of the groups were made regarding pathological features of SLN positive patient who did and did not undergo ALND. Menopause, tumor size, tumor stage, tumor type, tumor grade, lymphovascular invasion and receptor status had no effect on whether ALND was performed or not. However patients who had DCIS present

Table 2. Comparison of Post Operative Outcomes of Both the Groups

	PRE Z0011	POST Z0011	P value
# of positive SLNs	38 (25.7%)	34 (21.0%)	0.392
Median SLNs removed	2	2.3	0.789
# of ALNDs performed	38 (25.7%)	6 (3.7%)	<0.001
Median LNs removed in ALND	19	15	0.454
Median LNs removed Overall	6	2	<0.001
Median operating time	80min	60min	0.003
Length of hospital stay	2.1	1.3	<0.001

Table 3. Comparison of Clinicopathologic Features of SLN Positive Patient Who Did and Did Not Undergo ALND before and after Z0011

	Pre Z0011 (n=148)			Post Z0011 (n=162)		
	ALND (n=38)	No ALND (n=110)	P value	ALND (n=6)	No ALND (N=156)	P value
Median Age (y)	52	49.5	0.494	48.5	49	0.698
Menopause Status						
Pre	16	51	0.922	4	79	0.73
Post	22	59		2	77	
Mean Tumor Size	20	19	0.823	15	19	0.303
Clinical Stage						
T1	13	42	0.433	2	63	0.24
T2	13	31		0	44	
Pathological Tumor Size	22.8	26.4	0.154	28	24.6	0.481
Pathological T Stage						
T1	14	31	0.472	1	50	0.756
T2	22	71		5	85	
Histology						
Ductal	33	95	0.854	6	138	0.996
Lobular	3	5		0	4	
Others	1	10		0	11	
Grade						
1	3	0	0.026	0	3	0.464
2	20	51		4	61	
3	14	56		2	83	
Receptor Status						
ER +ve	31	76	0.138	4	120	0.781
ER -ve	5	32		2	33	
PR +ve	28	66	0.137	5	90	0.244
PR -ve	8	42		1	61	
H2N +ve	9	19	0.554	1	31	0.732
H2N -ve	25	70		5	106	
LVI						
Present	2	7	0.953	2	13	0.038
Absent	35	105		4	143	
DCIS						
Present	19	32	0.037	5	63	0.039
Absent	19	78		1	91	
Median # SLN	2	2	0.562	4	2	0
No. of positive SLNs						
1	27	1	0	0	22	0
2	7	0		3	7	
>3	2	0		3	0	
Size of Sentinel LN	14.6	15.2	0.905	11.8	15.8	0.134
Intraoperative Nodal Assessment	38	110	1	6	156	1

were more likely to undergo ALND in both the pre and post Z0011 group (p value 0.037 and 0.039). Patients who had 2 or more positive lymph nodes definitely underwent ALND (p value 0.000). Lymph node size had no bearing on whether ALND was performed or not.

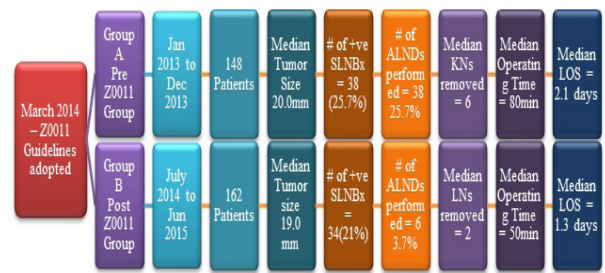


Figure 1. Flow Chart Depicting the Comparison of Both the Groups

## Discussion

Our study has shown that application of Z0011 guidelines has resulted in a significant change in practice at our institution. In SLN positive women, the rate of ALND decreased from 100 % in the year before the results were reported to 17 % in the post-Z0011 cohort. This is similar to what has been reported in other studies done after implementation of the Z0011 criteria. This change is significant because a significant number of breast cancer patients will be spared the morbidity of ALND, such as lymphedema (Lucci et al., 2007; Shih et al., 2009).

The median number of sentinel lymph nodes removed during sentinel dissection were 2. A lot of research is being done into how many lymph nodes should be removed. Some recommend only removing the nodes which take up the blue dye and are picked up by the radio frequency probe. Others now recommend removing at least 3 lymph nodes in all cases. At our institute we remove all the nodes which taken up the blue dye or are positive on the gamma probe. If only a single lymph node is positive no additional nodes are removed. If 2 LNs are positive then we remove another lymph node to remove at least 3 nodes in such patients. If on testing the three nodes are positive these patients are then subjected to undergo axillary clearance.

In our study we found that 82 % of breast cancer patients who had positive lymph nodes could be spared an ALND based on ACOSOG Z0011 criteria. This is in line with other single-institution experiences who have reported similar rates (Caudle et al., 2011; Guth et al., 2012). From the perspectives of these women spared an ALND and its concomitant morbidity (i.e., lymphedema, paresthesias), ACOSOG Z0011 is clearly a practice-changing trial (Lucci et al., 2007; and Shih et al., 2009).

Although the follow-up period for the current study is too short to determine lymphedema rates, a previous report of patients enrolled on the Z0011 study showed that lymphedema rates were lower in the SLND alone group (2 vs. 15 %). In one case-control study comparing medical costs in the 2 years after breast cancer diagnosis, total costs were \$22,153 higher in patients who developed lymphedema. Whereas there was a \$8,560 difference in cancer-related costs (p = 0.008), there was a \$14,600 difference between the groups in non-cancerrelated costs, such as treatment for infections and physical therapy (p = 0.001) (Shih et al., 2009). Thus, sparing breast cancer patients from ALND should decrease morbidity related to

ALND, which translates into cost savings.

Further savings should result from the decreased use of intraoperative nodal assessment and the corresponding decreased operative time for patients with negative SLNs. Another important aspect was that decreased rate of ALND leads to decreased post op hospital stay. Our median hospital stay reduced from 2.1 days to 1.3 days in all patients following the Z0011 criteria. These observations are vital in an era that emphasizes cost containment and clinician productivity.

There are a few limitations to our study. We only did a short follow up of our patients. Although our patients are being prospectively followed up but the real oncological outcomes of the Z0011 guidelines in terms of recurrence and overall survival cannot be answered by the current study. Also, the study was done only on tumors less than 5cm in size and the impact of Z0011 guidelines on tumors above this size remains unclear.

In conclusion, the ACOSOG Z0011 trial has been practice-changing at our institution. Implementation of the new guidelines has led to a significant reduction in the number of axillary nodes removed. There is a decrease in the total number of ALNDs performed which will result in lesser incidence of post op complications. There is definite advantage in terms of lesser operative time and reduced hospital stay although the exact cost benefit of this was not measured.

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#### Conflict of interest

There are no conflict of interests.

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