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Axillary dissection and nodal irradiation can be avoided for most node-positive Z0011-eligible breast cancers: a prospective validation study of 793 patients

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Abstract

Objective—To determine rates of axillary dissection (ALND) and nodal recurrence in patients eligible for ACOSOG Z0011.

Summary Background Data—Z0011 demonstrated that patients with cT1-2N0 breast cancers and 1–2 involved sentinel lymph nodes (SLNs) having breast-conserving therapy (BCT) had no difference in locoregional recurrence or survival after SLN biopsy alone or ALND. The generalizability of the results and importance of nodal radiotherapy (RT) is unclear.

Methods—Patients eligible for Z0011had SLN biopsy alone. Prospectively defined indications for ALND were metastases in ≥3 SLNs or gross extracapsular extension. Axillary imaging was not routine. SLN and ALND groups and radiation fields were compared with chi-square and t-tests. Cumulative incidence of recurrences was estimated with competing risk analysis.

Results—From 8/2010–12/2016, 793 patients met Z0011 eligibility criteria and had SLN metastases. 130 (16%) had ALND; ALND did not vary based on age, estrogen receptor, progesterone receptor, or HER2 status. 5-year event-free survival after SLN alone is 93% with no isolated axillary recurrences. Cumulative 5-year rates of breast+nodal and nodal+distant recurrence were each 0.7%. In 484 SLN-only patients with known RT fields (103 prone, 280 supine tangent, 101 breast+nodes) and follow-up≥12 months, the 5-year cumulative nodal recurrence rate was 1% and did not differ significantly by RT fields.

Conclusions—We confirm that even without preoperative axillary imaging or routine use of nodal RT, ALND can be avoided in a large majority of Z0011-eligible patients with excellent

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regional control. This approach has the potential to spare substantial numbers of women the morbidity of ALND.

Introduction

Management of the breast cancer patient with clinically negative (cN0) axillary lymph nodes has evolved over the past 2 decades from the routine use of axillary lymph node dissection (ALND) to sentinel lymph node (SLN) biopsy alone, reserving ALND for those with positive SLNs.[1] Management evolved further when the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that ALND need not be routine for patients with positive SLN; 889 patients with cT1-2N0 breast cancers and 1–2 positive SLN treated by breast-conserving therapy (BCT) with whole breast irradiation (WBRT) were randomized to SLN biopsy alone vs ALND.[2] At 6.3 years' follow-up, there were no differences in nodal recurrence (< 1% in both arms) or in any category of survival.[3] Z0011 was practice-changing but generated controversy. Critics suggested that these results may not be widely applicable and that the Z0011 patients were not representative of breast cancer patients as a whole because the majority of those enrolled were postmenopausal women with estrogen receptor (ER) positive cancers. There were also concerns that follow-up was insufficient, and that although Z0011 specified the use of tangent field irradiation alone, the low rates of nodal recurrence observed after SLNB alone were in part due to the use of nodal RT in a proportion of the study patients.[4, 5]

Beginning in 2010, we prospectively applied the Z0011 eligibility criteria in our clinical practice to all cN0 patients undergoing BCT with planned WBRT. We have previously reported that among our first 287 Z0011-eligible patients, 84% avoided ALND.[6] Here we report our expanded series of 793 consecutive Z0011 patients, focusing on the rate of ALND and on locoregional outcomes, stratified by type of RT.

Methods

In August 2010 we began to apply the results of ACOSOG Z0011 to the management of the axilla at Memorial Sloan Kettering Cancer Center. Women with cT1-2N0 invasive breast cancers undergoing BCT and having 1–2 positive SLN by routine hematoxylin and eosin (H&E) staining had SLNB only. Indications for ALND were prospectively defined as metastases in 3 or more SLN, matted nodes, or nodes with gross extracapsular extension.

Preoperative axillary imaging was not routine. If axillary imaging prior to referral showed that 1–2 nodes were abnormal, needle biopsy was not performed. When ≥ 3 abnormal nodes, were seen, a fine needle aspiration (FNA) of the most suspicious node was performed and, if malignant, ALND was performed. Patients with cN0 disease but biopsy-proven nodal metastases were managed with SLN biopsy as above, and have been reported previously.[7] Intraoperative SLN frozen section was eliminated, and patients were advised that a second surgery for ALND might be necessary. Management no longer employed the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram to estimate the risk of additional positive nodes after SLNB.[8] We anticipated that all patients would receive the adjuvant systemic therapy and WBRT that are part of standard care for node-positive patients

undergoing BCT. ALND remained standard management for SLN-positive patients undergoing mastectomy, and those with palpable nodal metastases. To mirror the Z0011 eligibility criteria, we excluded all patients receiving neoadjuvant therapy and all patients with nodal disease detected only by immunohistochemistry. This study was approved by the MSKCC Institutional Review Board.

We prospectively collected clinical and demographic data for all eligible patients treated by 14 different breast surgeons during the study period. Positive ER and progesterone (PR) receptor were defined as the presence of staining in ≥ 1% of tumor cells. HER2 positivity was defined as 3+ staining by immunohistochemistry and/or a FISH ratio > 2. Data on RT fields were obtained from radiation treatment summaries and/or port films. Nodal RT was defined as inclusion of the ipsilateral level III axillary and supraclavicular nodes, with or without internal mammary nodes, within the portals.

Chi-square tests and t-tests were used to compare characteristics of the SLN and ALND groups and radiotherapy fields. Competing risk analysis was used to estimate the cumulative incidence of distant, breast + nodal, breast only, and nodal + distant recurrences from the time of surgery.[9] All statistical analysis was performed with SAS 9.4 (SAS Institute, Cary, NC) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) statistical software. P-values were 2 sided, and values of < 0.05 were considered significant.

Results

From August 2010 through December 2016, 793 patients met Z0011 eligibility criteria, had BCT, and had SLN metastases. Patient characteristics are summarized in Table 1. The median patient age was 58 years, the median clinical tumor size was 1.7 cm, and 84% of patients had hormone receptor positive, HER2 negative cancers. Systemic adjuvant therapy was given to 97% of patients and RT to 94%. Median follow-up for the entire cohort is 29 months (range 2–76).

130 (16%) patients had ALND, most commonly for metastases in ≥ 3 sentinel nodes (n = 88) or for SLN with extracapsular tumor extension (n = 34). Surgeon/patient preference accounted for ALND in 8 patients otherwise eligible for SLNB alone, with 6 of these 8 in our initial 2 years' experience. One or more "high-risk" features, defined as age < 50 years, HER2 positive, or triple negative breast cancer were present in 288 patients. The remaining 505 patients were age 50 or older with hormone receptor positive, HER2 negative cancers. The frequency of ALND did not differ significantly for the "high-risk" and non-high risk groups, 16% vs 17%, respectively (p = 0.81).

In comparing the patients who had ALND and those who did not (Table 1), there were no significant differences in age, tumor histology, tumor grade, or biologic subtype (as approximated by ER, PR, and HER2 status). Patients requiring ALND had significantly larger tumors (2.2 versus 1.6 cm, p < 0.0001) and were significantly more likely to have SLNs with microscopic extracapsular tumor extension (82% versus 31%, p < 0.0001). More patients in the ALND group received chemotherapy plus endocrine therapy, and fewer received endocrine therapy alone, reflecting their higher risk for distant recurrence (p =

0.001). Only 3% of patients in each group did not receive some form of systemic therapy. There were no differences between groups in the use of RT (p = 0.13).

The 5-year event-free survival for the SLNB-only group is 93% (95% confidence interval [CI] 89%–94%) There have been no first-event (isolated) axillary recurrences. Among 8 nodal recurrences, 4 were coincident with ipsilateral breast tumor recurrence and 4 were synchronous with distant metastases. Among the 4 patients with breast and axillary nodal recurrence, 3 had not received radiotherapy and the median time to recurrence was 9.5 months (range 3–27). Among the 4 patients with nodal and distant recurrence, 1 was axillary, 2 were supraclavicular, and 1 was supraclavicular and internal mammary. The cumulative incidence of recurrence by type of event is shown in Figure 1. Distant recurrence was the most common and had a 5-year cumulative incidence of 5% (95% CI 3%–7%). The median time to distant recurrence was 18.5 months (n=24, range 1–67 months). The 5-year cumulative rates of breast + nodal, and nodal + distant recurrences were 0.7% (95% CI 0–1%) and 0.7% (95% CI 0–2%), respectively, with a median time to any nodal recurrence of 25 months (n= 8, range 3–67months). The 5-year rate of breast-only recurrences was 1.6% (95% CI 0–3%). At last follow-up, 746 patients (94%) were alive and free of breast cancer, 18 were alive with metastatic breast cancer, 11 had died of breast cancer, 7 were alive with other cancers, 6 had died of other cancer while free of breast cancer, and 5 were dead of an unknown cause.

To better stratify the risk of nodal recurrence, we examined a subset of 509 patients treated with SLNB alone with known RT fields and follow-up of at least 12 months. We excluded 25 who received non-standard treatment (23 with no RT and 2 with partial breast RT), leaving 484 for analysis. Of these, 103 (21%) had prone breast RT, 280 (58%) had supine tangent breast RT, and 101 (21%) received breast and nodal RT. Patients selected for nodal RT had more high-risk features than those treated prone or with tangent fields alone (Table 2). At a median follow-up of 37 months (range 12–75) there have been 5 nodal recurrences among this subset; 4 nodal and distant and 1 breast and axillary. The 5-year cumulative rate of nodal recurrence was 1% (95% CI 0–2%) and did not differ significantly by RT fields (Table 2). Nodal recurrence was seen in 1% of patients treated prone, 1.4% of those treated supine, and in none of those receiving breast + nodal RT.

Discussion

Here we demonstrate in a large series of patients, selected only on the basis of Z0011 eligibility criteria, that the morbidity of ALND was avoided in 84%. The results of retrospective studies which have addressed this question, summarized in Table 3, vary widely, with ALND avoided in 9–75% of patients.[5, 10–13] This variation is not at all surprising, as these studies vary by denominator (all patients vs all node-positive patients vs all node-positive patients having BCT), by operation (SLNB versus ALND), and by the failure to distinguish between SLN and non-SLN metastases. The Z0011 eligibility criteria for omission of ALND specified metastases in ≤ 2 *SLN* and since additional nodal metastases were found in 27% of patients randomized to ALND, it can be assumed that an equal number of patients randomized to the SLNB-only arm had additional axillary metastases which were successfully controlled without further surgery.[3] Retrospective

studies which do not distinguish between metastases in the SLN and the non-SLN minimize the potential benefit of adopting the Z0011 approach.

Some controversy surrounds the subject of preoperative axillary imaging, which we have elected not to do in our Z0011-eligible patients. Among 425 of our Z0011-eligible patients with abnormal axillary imaging (on mammography, ultrasound, or MRI) 70% had 1–2 positive nodes and could avoid ALND.[14] Among 141 of our Z0011-eligible patients with a positive image-guided axillary needle biopsy, 47% had 1–2 positive nodes and could avoid ALND.[7] These data confirm that preoperative axillary imaging and even a positive axillary needle biopsy are inadequate to make the decision for ALND, and that for Z0011-eligible patients, a negative clinical examination of the axilla is sufficient.

In our prospective study of Z0011-eligible patients, only the number of SLN metastases or extracapsular extension could be considered in the decision to perform ALND, and we did not apply any additional “high-risk” selection criteria such as patient age, ER status, or HER2 status. This decision was based on previous studies which found that nodal recurrence after ALND was not related to patient age or hormone receptor status.[15, 16] Our results support that decision; although our study, like Z0011, largely comprised patients who were older and ER positive, the rate of ALND was no higher among patients who were “high risk” by younger age and/or ER negative and/or HER2 positive disease. These results confirm previous work demonstrating that patients at higher risk for systemic relapse do not necessarily have a heavier nodal disease burden.[17, 18] These results are also consistent with the 10-year outcomes of the Z0011 trial, in which younger age and ER negativity were significantly associated with locoregional recurrence, but event rates did not differ between the ALND and SLNB-only arms, and the majority of the locoregional events were ipsilateral breast, not nodal, recurrences.[3] Further, an exploratory analysis of Z0011 has found no differences in 10-year overall survival by ER status or by axillary treatment.[19]

To what extent did node field RT contribute to the excellent locoregional control of Z0011? Although the Z0011 protocol specified RT to breast only, an audit by Jagsi et al.[20] of a subset of Z0011 patients for whom complete RT data were available found that 19% received nodal RT and that nodal RT was equally frequent in the ALND and SLNB-only arms. Like Z0011, 21% of our patients received nodal RT, and the use of nodal RT increased with the number of positive SLNs. Risk factors for local recurrence, including extracapsular extension, lymphovascular invasion, and larger tumor size were more common among our patients receiving nodal RT. Of note, our patients treated by WBRT without nodal RT were not a uniquely favorable subgroup: about half had lymphovascular invasion and 17% (prone RT) to 28% (supine tangent RT) had microscopic extracapsular tumor extension in their SLN, despite which nodal recurrence of any type (isolated or combined) was rare. Although the AMAROS trial[21] demonstrated that locoregional recurrence and survival did not differ among patients with 1–2 SLN metastases randomized to nodal RT versus ALND, the results of ACOSOG Z0011 and our own study strongly suggest that routine nodal RT for SLN-positive patients treated with SLNB alone need not be mandatory.

To our knowledge, this is the first confirmation of the findings of ACOSOG Z0011 in clinical practice and indicates that nodal recurrence rates are extremely low despite relatively

infrequent use of nodal RT. The strengths of this study include its large patient population, prospective design, uniform treatment algorithm, and detailed information regarding the use of systemic therapy and RT fields. Moreover, the similar frequencies of nodal RT use in our study (21%) and ACOSOG Z0011(19%) indicate that radiation oncology practices between the two studies were similar. Our study has some limitations. Single-institution data from a group of high-volume breast surgeons may not be widely representative, but given that our results mirror those of ACOSOG Z0011 (in which participant surgeons varied widely by geography and case volume), we do not think that this is a major limitation. Our median follow-up of 3 years (used to calculate rates of nodal recurrence) is relatively short, but since the median time to regional node recurrence in the ACOSOG Z0011 trial was 4 years and only a single nodal recurrence was observed after 76 months,[3] we are highly unlikely to observe a substantial increase in isolated nodal recurrences with further follow-up. Finally, we must emphasize that our results cannot be extrapolated beyond the Z0011 selection criteria (cT1-2N0, BCT, 1–2 SLN+, WBRT, systemic therapy). New trials are asking whether ALND can be avoided for SLN-positive patients treated by mastectomy[4] or for patients who are SLN-positive after neoadjuvant chemotherapy,[22] and it remains unclear if ALND can be avoided for SLN-positive patients treated with partial breast RT or with no RT at all. For these patients, a positive SLN remains at present an indication for ALND.

Conclusions

Here we confirm the findings of ACOSOG Z0011 in a large prospective study, and demonstrate that without preoperative axillary imaging, the use of additional selection criteria, or routine use of nodal RT, ALND can be avoided in a substantial majority of Z0011-eligible breast cancer patients with excellent local, regional, and distant control of disease. Wider adoption of the ACOSOG Z0011 algorithm has the potential to spare a substantial number of women the morbidity of ALND.

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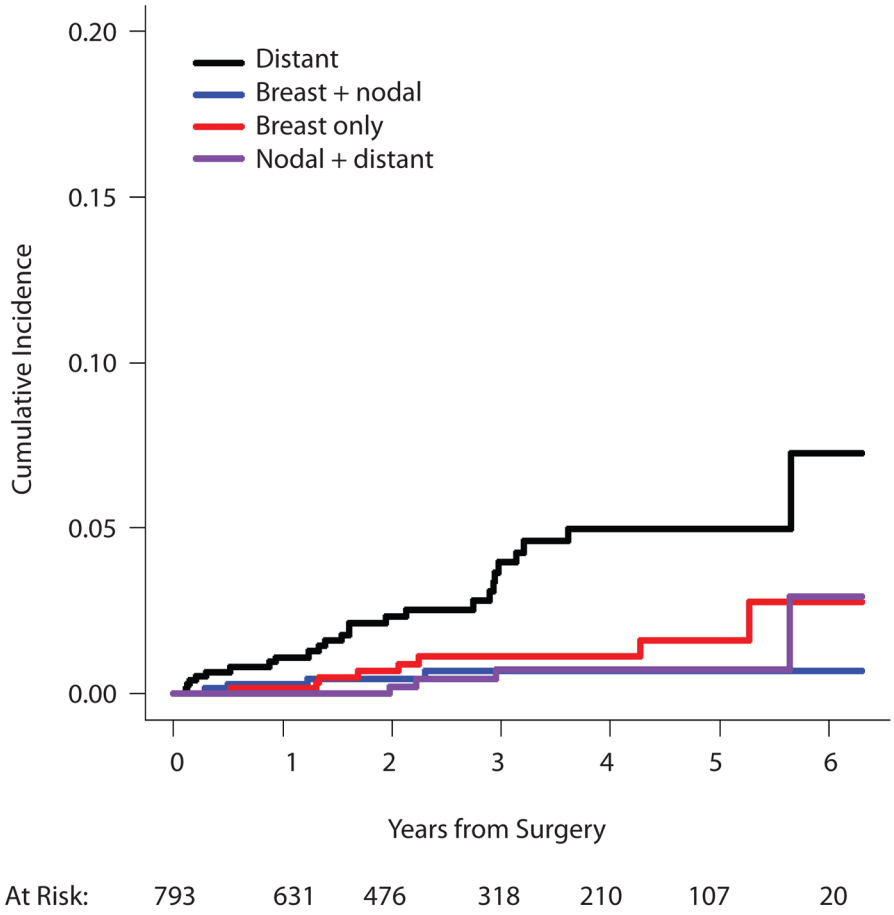

Figure 1.
Cumulative incidence by type of event (whole dataset, n = 793)

Table 1

Patient characteristics

Characteristic	Total	ALND	No ALND (SLNB only)	
	(n = 793)	(n = 130)	(n = 663)	p-value
Age (median, range)	58 years (30–92)	57 years (35–86)	58 years (30–92)	0.87
Clinical tumor size (median, range)—from imaging	1.7 cm (.2–6.5)	2.0 cm (.6–6.5)	1.6 cm (.2–6)	0.01
Histology				0.32
Ductal	689 (87%)	108 (83%)	581 (88%)	
Lobular	71 (9%)	16 (12%)	55 (8%)	
Mixed D&L	27 (3%)	4 (3%)	23 (3%)	
Other (metaplastic, mucinous)	6 (0.8%)	2 (2%)	4 (0.6%)	
Grade				0.57
1	39 (5%)	5 (4%)	34 (5%)	
2	440 (55%)	69 (53%)	371 (56%)	
3	305 (38%)	55 (42%)	250 (38%)	
Unknown	10 (1%)	1 (1%)	8 (1%)	
Subtype				0.18
ER or PR+/HER2−	668 (84%)	110 (85%)	558 (84%)	
ER or PR+/HER2+	59 (7%)	10 (8%)	49 (7%)	
ER PR−/HER2+	20 (3%)	0 (0%)	20 (3%)	
Triple negative	46 (6%)	10 (8%)	36 (5%)	
No. positive SLNs (median, range)	1 (1–11)	3 (1–11)	1 (1–2)	<.0001
LVI present	464 (59%)	84 (65%)	380 (57%)	0.12
ECE *				<.0001
None	483 (61%)	23 (18%)	460 (69%)	
≤ 2 mm	141 (18%)	28 (14%)	113 (17%)	
> 2 mm	169 (21%)	79 (61%)	90 (14%)	
Path T Stage				<.0001
1	504 (64%)	56 (43%)	448 (68%)	
2	286 (36%)	73 (56%)	213 (32%)	
3	3 (0%)	1 (0%)	2 (0%)	
Path Tumor Size (median, range)	1.7 cm (.1–5.7)	2.2 cm (.4–5.7)	1.6 cm (.1–5.2)	<.0001
Path Stage				<.0001
1	129 (16%)	0 (0%)	129 (19%)	
2	592 (75%)	60 (46%)	532 (80%)	
3	72 (9%)	70 (54%)	2 (0%)	
Adjuvant Tx				0.001
No chemo or endo	17 (2%)	3 (2%)	14 (2%)	
Chemo + endocrine	513 (65%)	101 (78%)	412 (62%)	

Characteristic	Total	ALND	No ALND (SLNB only)	
	(n = 793)	(n = 130)	(n = 663)	p-value
Chemo only	73 (9%)	12 (9%)	61 (9%)	
Endocrine only	186 (23%)	13 (10%)	173 (26%)	
Unknown chemo/endo	4 (0%)	1 (1%)	3 (0%)	
RT	743 (94%)	118 (91%)	625 (94%)	0.13
No RT	45 (6%)	11 (8%)	34 (5%)	
Unknown RT	5 (1%)	1 (0%)	4 (1%)	

ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; ER, estrogen receptor; PR, progesterone receptor; SLN, sentinel lymph node; LVI, lymphovascular invasion; ECE, extracapsular extension; RT; radiation therapy

Note: p-values are based on complete data.

* missing 10

Table 2

Patient characteristics by radiotherapy fields

Radiation therapy (n = 484)				
	Prone breast	**Supine breast**	**Breast + nodes**	**p-value**
# patients (%)	103 (21%)	280 (58%)	101 (21%)	
Age (median)	55	58	56	0.28
pT size (cm; median)	1.5	1.6	1.8	0.08
# SLN+ (median)	1	1	1	0.0004
LVI present (%)	50 (49%)	157 (56%)	73 (72%)	0.002
ECE present (%) *	19 (18%)	75 (27%)	55 (54%)	<.0001
Stage > 2A	26 (25%)	87 (31%)	41 (41%)	0.06
nodal relapse # (%)	1 (1%)	4 (1.4%)	0	.544 **

pT, primary tumor; SLN, sentinel lymph node; LVI, lymphovascular invasion; ECE, extracapsular extension;

* Uses all categories of ECE size

** Gray's test

Table 3

Elimination of axillary lymph node dissection using ACOSOG Z011 eligibility criteria

Author	Number of Patients	No ALND
Ngui[11]	119	22%
Verhuevel[12]	916	61%
Delpech[10]	125	70%
Yi[13]	488	75%
Guth[5]	55	9%
Present Study	793	84%

ACOSOG, American College of Surgeons Oncology Group