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Age and Receptor Status Do Not Indicate the Need for Axillary Dissection in Patients With Sentinel Lymph Node Metastases

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Abstract

Background—ACOSOG Z0011 demonstrated the safety of omitting axillary dissection (ALND) in women with <3 positive sentinel lymph nodes (SLNs) undergoing breast-conservation therapy (BCT). Since most were postmenopausal with ER-positive cancers, applicability to younger patients or those with triple-negative (TN) or HER2 overexpressing (HER2+) tumors remains controversial.

Methods—From 8/2010–12/2015, patients undergoing BCT for cT1-2N0 disease and found to have positive SLNs were prospectively followed. ALND was indicated for >2 positive SLNs or gross extracapsular extension. Clinicopathologic characteristics, axillary surgery, nodal burden, and outcomes were compared between high-risk (TN, HER2+, or age<50 years), and the remaining patients, termed average-risk.

Results—Among 701 consecutive patients, 242 (35%) were high-risk: 31 (13%) TN, 48 (20%) HER2+, 130 (54%) age<50, and 33 (14%) >1 high-risk feature; 459 (65%) were average-risk. High-risk patients were younger, with higher-grade tumors ($p<0.0001$), and more often had abnormal nodes imaged ($p=0.02$). SLNB alone was performed in 85% high-risk vs. 82% average-risk cases ($p=0.39$): median 4 vs. 3 SLNs excised ($p=0.04$), and median of 1 positive SLN in both groups. 62% high-risk vs. 65% average-risk ($p=0.8$) had additional positive nodes at ALND, with a median of 3 positive nodes in both groups. At median follow-up of 31 months, there were no isolated axillary recurrences.

Conclusions—ALND was no more likely to be indicated in high-risk patients. In patients undergoing ALND, nodal burden was similar. ALND is not indicated based upon age or subtype in patients otherwise meeting Z0011 clinical eligibility criteria.

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Keywords

ACOSOG Z0011; sentinel lymph node biopsy; axillary dissection; high-risk; nodal burden

INTRODUCTION

The presence of axillary metastases is an important prognostic factor in invasive breast cancer. The approach to the axilla has evolved significantly in the past decade, with sentinel lymph node biopsy (SLNB) becoming the preferred method for axillary staging.^{1–3} The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated no difference in locoregional recurrence (LRR) or overall survival among women with T1–T2, clinically node-negative (cN0) tumors undergoing breast-conserving surgery followed by whole breast radiation therapy (BCT) and systemic therapy when those with < 3 positive sentinel lymph nodes (SLNs) were managed with SLNB alone, compared to SLNB and axillary lymph node dissection (ALND).⁴ The After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial similarly showed non-inferiority of SLNB and axillary radiation therapy compared to ALND in patients with < 3 positive SLNs.⁵ Evidence provided by the ACOSOG Z0011 trial has led to omission of ALND and its associated morbidity in many women.⁶ Despite this paradigm shift, the applicability of these results to patients at higher risk of distant metastases, including younger women and those with estrogen receptor-negative (ER–) or HER2 overexpressing (HER2+) disease has been questioned, as most women in the Z0011 trial were post-menopausal and had ER-positive (ER+) disease.⁴ We sought to compare the need for ALND (> 2 positive SLNs, gross ECE) in high-risk patients (defined as those with triple-negative (TN) or HER2+ breast cancers or those less than 50 years of age), to the use of ALND in those lacking these high-risk features, in a prospective, consecutive series of cT1–2N0 patients with positive SLNs. Additionally, we compared the residual nodal disease burden between groups in those requiring ALND.

METHODS**Patient Cohort**

Beginning in August 2010, consecutive patients with clinical T1–T2, cN0 invasive breast cancer undergoing BCT found to have SLN metastases by routine hematoxylin and eosin (H&E) staining at Memorial Sloan Kettering Cancer Center were managed without ALND if metastases were present in 1–2 SLNs, and underwent ALND if ≥ 3 positive SLNs or gross extracapsular extension (ECE) was present. Intraoperative frozen section was not utilized, and ALND was performed as a second separate procedure when indicated. Management of nodes with microscopic ECE was by surgeon preference. Patients were prospectively entered into a registered database. Patients receiving neoadjuvant chemotherapy, those with SLN metastases detected only by immunohistochemistry, and those requiring mastectomy after attempted breast conservation were excluded.

After institutional review board approval, patients treated between August 2010 and December 2015 were identified. Those with TN or HER2+ tumors, or less than 50 years of age at diagnosis were categorized as high-risk, while the remainder of the population was

termed average-risk. Hormone receptor positivity was defined as 1% or more of cells staining for ER or progesterone receptor. HER2 positivity was defined as 3+ staining by immunohistochemistry or FISH amplification with value > 2.0.

Variables Studied

Standard clinical and pathologic data were collected, including patient age, clinical presentation of disease, tumor size, grade, and final tumor and nodal pathologic findings. Rates of administration of systemic therapies were assessed. Outcomes of interest were the rates of ALND and the number of positive nodes at ALND.

Statistical Analysis

Comparisons between high-risk and average-risk groups were made using the chi-square test and two-sample t-test. All statistical analysis was done using SAS 9.2 (SAS Institute, Cary, NC), and p-values < 0.05 were considered significant.

RESULTS

From August 2010 to December 2015, 701 T1–T2, cN0 patients with positive sentinel nodes were identified. Of these, 242 (35%) were high-risk, including 31 (13%) TN cases and 48 (20%) HER2+ cases among women 50 years of age. Among patients < 50 years of age, 130 (54%) had hormone receptor positive/HER2-negative disease, 11 (5%) were TN, and 22 (9%) were HER2+. The remaining 459 (65%) cases were termed average-risk.

Table 1 summarizes clinicopathologic characteristics of both groups. Preoperative axillary imaging was not standard and was performed prior to referral or by individual physician preference. Abnormal nodes on any imaging modality were more frequently identified among high-risk patients (30% high-risk vs. 22% average-risk, $p = 0.02$), but preoperative nodal biopsy was done in a similar proportion of patients (7% high-risk vs. 5% average-risk, $p = 0.31$). Although tumors were more frequently palpable (51% vs. 36%, $p < 0.0001$) and appeared larger on imaging (median 1.9 cm vs. 1.6 cm, $p = 0.0001$) in the high-risk group, pathologic tumor size was not significantly different between the 2 groups (1.8 cm high-risk vs. 1.7 cm average-risk, $p = 0.44$). High-risk patients were more likely to have tumors with high nuclear grade ($p < 0.0001$), with 56% grade 3 cases compared to 27% in the average-risk group, and were less likely to have > 2 mm of microscopic ECE than average-risk patients (17% vs. 24%, $p = 0.0497$).

A median of 4 vs. 3 SLNs were excised in the high-risk vs. average-risk groups ($p = 0.04$), with a median of 1 positive SLN in both groups. 205 (85%) high-risk patients and 377 (82%) average-risk patients met criteria for SLNB alone ($p = 0.39$). Among 37 (15%) high-risk and 82 (18%) average-risk patients who had ALND ($p = .039$), indications were similar, performed for more than 2 positive SLNs in 70% high-risk vs 62% average-risk cases and for gross ECE in 24% high-risk vs. 30% of average-risk cases ($p = 0.69$) (Table 2). The median number of additional nodes excised at ALND was 15 (range 4–52) in the high-risk and 14 (0–53) in the average-risk group ($p = 0.35$) (Table 2). Additional positive nodes were found in 62% of high-risk vs 65% of average-risk cases ($p = 0.8$), with a median of 3 additional positive nodes in both groups (Table 2). There were 10 patients (5 high-risk, 5

average-risk) who did not undergo ALND despite having more than 2 positive SLNs: 2 patients refused, 4 had significant medical comorbidities felt to preclude further surgery, and 4 cases were deferred per the surgeon's clinical judgment.

Adjuvant therapies and outcomes were assessed in patients undergoing SLNB alone who completed surgery in 2014 or prior ($n = 470$) to allow a follow-up of at least 12 months; 166 patients were high-risk and 304 were average-risk. Adjuvant chemotherapy was given to 156 (95%) high-risk vs. 195 (64%) average-risk patients ($p < 0.0001$) and endocrine therapy to 116 of 122 (95%) high-risk and 291 of 302 (96%) average-risk patients who were hormone receptor-positive ($p = 0.54$). HER2-targeted therapy was received by all HER2+ patients. Systemic adjuvant therapy status was unknown in 1 high-risk and in 3 average-risk patients. Adjuvant radiotherapy was given to 440 patients (94%), including 161 (97%) high-risk and 279 (92%) average-risk patients ($p = 0.03$). Whole breast irradiation was given to 422 (96%) patients, 81 (18%) patients had additional nodal irradiation, 1 patient received intraoperative radiotherapy, and data regarding radiated fields were unavailable in 17 (4%) of cases. The use of nodal irradiation did not differ significantly between the average- and high-risk groups (21% high-risk vs. 16% average-risk, $p = 0.24$). At median follow-up of 34 (high-risk) vs. 30 (average-risk) months (range 1–63), there have been no isolated axillary recurrences in either group. Two patients in each group have had in-breast recurrence only, and 2 patients in each group have had synchronous axillary and breast recurrences. Two patients in the high-risk group have had synchronous axillary and distant recurrence and 1 patient had synchronous breast and distant recurrence. Among the 4 high-risk patients with axillary recurrences, 1 was TN, 2 were younger than 50 years of age, and one was younger than 50 years of age with TN cancer; none were HER2+. There have been no combined local/distant recurrences in the average-risk group.

DISCUSSION

Our study provides evidence in a large consecutive cohort of T1–2 cN0 patients prospectively treated over a 5-year period, that younger patients and those with TN or HER2 overexpressing cancers are no more likely to require ALND due to the presence of 3 positive SLNs or gross ECE than those 50 years of age with ER+/HER2-negative breast cancer. A study from the National Cancer Database including 74,309 patients meeting Z0011 eligibility criteria from 1998 to 2011 showed that overall rates of SLNB alone for patients with node-positive breast cancer markedly increased in the post-Z0011 era, rising from 6% in 1998 to 56% in 2011. However, among the subset of 9860 patients treated post-Z0011, independent predictors of ALND included TN receptor status ($p < 0.001$) and age younger than 50 years ($p = 0.006$).⁷ Our findings provide compelling evidence for a change in this approach, with only 15% of high-risk patients in our study having indications for ALND.

Past studies of SLNB followed by ALND for metastases in 1 or 2 SLNs report an incidence of non-SLN metastases of 27 to 46%^{2,4,8,9}, increasing to as high as 70% in patients with 3 or more positive SLNs.¹⁰ These reported rates are from populations primarily consisting of hormone receptor positive, older women who constitute the majority of breast cancer patients. In a retrospective study of 183 high-risk patients, also defined as HER2+, TN, or

age < 50 years, 125 patients met Z0011 clinical eligibility criteria (cT1-T2 cN0 with positive SLNs). Of these, 84% underwent ALND, and only 38% had non-SLN involvement,¹¹ supporting our findings that patient and tumor features associated with a higher risk of distant metastases are not indicative of a heavy axillary tumor burden. While younger patients and those with hormone receptor-negative tumors are known to have tumors with a more aggressive biology and poorer prognosis^{12–15}, among those with indications for ALND in our study, a similar residual nodal disease burden, with a median of 3 additional positive nodes, was present in both the high-risk and average-risk groups.

Multiple studies have demonstrated that patients with TN tumors are significantly less likely than those with other tumor subtypes to have metastases in 4 or more axillary nodes.^{12,13,16,17} In a study of 284 women meeting Z0011 clinical eligibility criteria who underwent SLNB followed by ALND, not only was the likelihood of additional non-sentinel disease lowest among TN cases (21%), but all cases had fewer than 4 non-sentinel nodes involved when additional metastases were present.¹⁷ This study also found that age was not associated with having ≥ 4 positive nodes ($p = 0.6$).¹⁷

The literature on nodal involvement in patients with HER2+ tumors suggests these patients are more likely to have a heavier nodal burden. Gangi et al, in a study of 2967 patients undergoing any breast surgery with either SLNB or ALND, found that metastases in 4 or more nodes were present in 19% of HER2+ patients, with the lowest rate (9%, $p < 0.0001$) seen among TN cases. On multivariate analysis, after adjustment for size, grade, age, and presence of lymphovascular invasion, HER2+ subtypes were more likely to have ≥ 4 positive nodes (odds ratio [OR] 1.4; 0.9–2.3), while the TN subtype was the least likely (OR 0.5; 0.3–1.1, $p = 0.008$). Age < 50 years was also not predictive of having ≥ 4 positive nodes.¹⁸ Similarly, Wiechmann et al in a larger study including 6072 patients with stage I–III cancers, found that HER2+ patients were significantly more likely to have involvement of ≥ 4 lymph nodes than those with hormone receptor positive or TN cancers ($p < 0.0001$) after controlling for age, tumor size, lymphovascular invasion, and grade.¹⁶ Although the possibility of a greater nodal disease burden in HER2+ cases might raise concern about omission of ALND in patients with metastases in 1 or 2 SNs, this should be offset by the documented effectiveness of HER2 targeted therapy in combination with chemotherapy in eradicating nodal disease in the neoadjuvant setting.^{19–21} This is supported by our finding that none of the axillary recurrences occurred in HER2+ patients.

Along with having similar rates of ALND and equivalent nodal disease burden, LRR rates in the high-risk and average-risk patients are also comparable in this study. While the absence of any isolated axillary recurrences in our population with a median follow-up of 2.6 years is reassuring, further follow-up is necessary to determine the rate of regional failure in this group. However, the majority of recurrences in patients with HER2+ and TN disease occur within the first 5 years after initial diagnosis, suggesting that rates of isolated axillary failure are unlikely to increase dramatically with further follow-up.^{22–26}

The majority of recurrences in the high-risk patients in this study included distant metastases (71%). There were only 4 locoregional-only recurrences, and none were isolated axillary recurrences, emphasizing the importance of avoiding unnecessary surgical morbidity in

these patients.^{14,27,28} While ongoing follow-up will determine long-term rates of regional recurrence, the results of this study support the application of Z0011 results to patients otherwise meeting study clinical eligibility criteria, regardless of age or receptor status.

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Synopsis

Among 701 cT1-T2N0 BCT patients with positive SLNs, high-risk (triple-negative, HER2+, age<50) patients were no more likely to have 3 positive SLNs than average-risk patients, and had similar residual nodal burden at axillary dissection. No isolated axillary recurrences have occurred.

Table 1

Clinicopathologic characteristics of high-risk (hormone receptor-negative, HER2-amplified, or age < 50 years) and average-risk patients

Characteristic	High Risk (n = 242)	Average Risk (n = 459)	p
	Median (Range)	Median (Range)	
Age (years)	47 (30–83)	62 (50–92)	*
Clinical tumor size (cm)	2.0 (0.5–5.0)	2.0 (0.5–8.0)	0.26
Pathologic tumor size (cm)	1.8 (0.2–5.7)	1.7 (0.1–5.2)	0.44
	n (%)	n (%)	
Palpable tumor	124 (51%)	165 (36%)	< 0.0001
Abnormal nodes on imaging	73 (30%)	102 (22%)	0.02
Preoperative node biopsy done	16 (7%)	22 (5%)	0.31
Histology			
Ductal	217 (90%)	394 (86%)	0.15
Lobular or mixed	21 (9%)	62 (14%)	
Other	4 (2%) [‡]	3 (1%) [§]	
Nuclear grade			
1	8 (3%)	32 (7%)	< 0.0001
2	94 (39%)	295 (64%)	
3	135 (56%)	124 (27%)	
Not reported	5 (2%)	8 (2%)	
Extracapsular extension			
None	158 (65%)	261 (57%)	0.0497
2 mm	43 (18%)	86 (19%)	
> 2 mm	41 (17%)	112 (24%)	
Multifocal	26 (11%)	67 (15%)	0.15
Lymphovascular invasion	151 (62%)	257 (56%)	0.10

* No p-value calculated due to exclusive values in either group, by risk category definition

^{‡§} Other histologies: [‡]metaplastic (n = 4), [§]mucinous (n = 2), [§]neuroendocrine (n = 1)

Table 2

Pathologic nodal characteristics of high-risk and average-risk patients

SLNB			
	High Risk (n = 242)	Average Risk (n = 459)	p
	n (%)	n (%)	
# of positive SLNs			
1 or 2	211 (87%)	403 (88%)	0.82
3 *	31 (13%)	56 (12%)	
	Median (Range)	Median (Range)	
# SLNs excised	4 (1–18)	3 (1–17)	0.04
ALND			
	High Risk (n = 37)	Average Risk (n = 82)	p
	n (%)	n (%)	
Indication			
3 positive SLNs *	26 (70%)	51 (62%)	0.69
Gross ECE	9 (24%)	25 (30%)	
Clinical judgment	2 (5%)	6 (7%)	
Positive non-SLNs	23 (62%)	53 (65%)	0.8
	Median (Range)	Median (Range)	
# Additional positive nodes	3 (1–52)	3 (1–53)	0.43
# Additional nodes excised	15 (4–52)	14 (0–53)	0.35

SLNB, sentinel lymph node biopsy; SLNs, sentinel lymph nodes; ALND, axillary lymph node dissection; ECE, extracapsular extension

* n = 10 patients with 3 positive SLNs but ALND deferred, due to significant comorbidities (n = 4), patient refusal (n = 2), or clinical judgment (n = 4)