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ORIGINAL ARTICLE – BREAST ONCOLOGY

Applicability of the ACOSOG Z0011 Criteria in Women with High-Risk Node-Positive Breast Cancer Undergoing Breast Conserving Surgery

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ABSTRACT

Background. The relevance of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial in patients with high-risk breast cancer has been questioned. We hypothesize that Z0011 applies to women with HER2-positive disease (HER2+), triple-negative breast cancer (TNBC), and/or age <50 years at diagnosis (YA).

Methods. Women with node-positive HER2+, TNBC, or YA were identified from a prospectively maintained database. Patients were grouped based on Z0011 trial eligibility criteria into those meeting criteria (eligible) and those who did not (ineligible). Patient and tumor characteristics were compared; survival of those meeting Z0011 criteria was determined.

Results. We identified 186 node-positive women undergoing lumpectomy/radiation for high-risk breast cancer: 57 of 186 (31 %) HER2+, 55 of 186 (30 %) TNBC, 74 of 186 (40 %) YA. Overall, 125 of 186 (67 %) met Z0011 criteria. HER2-positivity was associated with the lowest rate of ineligibility compared with TNBC and YA (16 vs. 53 and 31 %, respectively, $p < 0.01$). Larger tumor size, high grade, extranodal extension, and high Ki67 were associated with Z0011 ineligibility. Among those who were eligible, 105 of 125 (84 %) had ALND and 48 of 125 (38 %) had involvement of nonsentinel nodes (NSLN); median number of NSLNs involved was one (range 1–3). With median follow-up of 5.5 years, there was no difference in survival between those who had ALND and those who did not. After patients with clinically palpable nodes were excluded, 125 of 149 (84 %) met criteria.

Conclusions. The Z0011 trial eligibility requirements apply to a significant proportion of patients with HER2+, TNBC, and YA. ALND can be avoided in 67 % node-positive cases and in 84 % of those with clinically negative nodes.

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The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that sentinel lymph node biopsy (SNB) without completion axillary lymph node dissection (ALND) in patients with clinical T1-2N0 breast cancer resulted in excellent local control without compromising survival.[1,2] Although the results of the trial triggered changes in the standard paradigm in the surgical management of axillary lymph nodes in breast cancer, there remain concerns that the large majority of the Z0011 study population included older patients with estrogen-receptor positive (ER+), less aggressive tumors and that the higher risk populations were underrepresented in the trial. Therefore, there is controversy whether ALND should be performed in these populations even if the eligibility criteria for the Z0011 trial have been met.

The purpose of this study was to determine how often the ACOSOG Z0011 eligibility requirements apply in patients with higher risk tumors, such as triple-negative (TNBC) and HER2-positive (HER2+) breast cancer, and/or young age at diagnosis (YA) and to examine the reasons for inapplicability of the trial in these subgroups of patients.

METHODS

A review of a prospectively maintained database was performed from January 1, 2000 to December 31, 2011 to identify patients with high-risk breast cancer undergoing breast conserving surgery at our institution who had at least one positive node identified by hematoxylin and eosin

(H & E) staining. High-risk breast cancer was defined as TNBC, HER2+, and age at diagnosis <50 among ER+/HER2-negative cases (YA). Patients undergoing mastectomy, those with nodal disease detected only by immunohistochemistry, and those with insufficient available pathologic data were excluded. Patient and tumor characteristics were reviewed and patients were categorized into two groups based on the Z0011 eligibility criteria: those who met eligibility criteria for the Z0011 trial and those who did not meet eligibility criteria. Eligibility criteria were determined from the ACOSOG Z0011 protocol. Patients were considered to be in the eligible group if they had clinical T1-2N0 invasive breast cancer treated with lumpectomy, SNB, and whole breast radiation and had 1–2 positive SLNs identified by H & E staining. Clinical status of the tumor size was based on physical exam and preoperative imaging modalities. Clinical status of the axillary lymph nodes was based on physical exam only. Patients were considered ineligible if they presented with clinical T3 lesions or clinically palpable nodes, received neoadjuvant therapy, did not have a SNB, were found to have gross extracapsular extension at the time of SNB, or had three or more positive SLNs. Reasons for ineligibility were documented. Groups were compared with regards to the following patient and tumor characteristics: age at diagnosis, tumor size, grade, presence of lymphovascular invasion (LVI), multifocality, number of nodes positive, size of the largest metastasis, presence of microscopic extranodal extension (ENE), Ki67, and ER, PR, and HER2 status. Factors associated with ineligibility were determined. Among patients who met the eligibility criteria, frequency of non-SLN involvement, frequency of ALND, and survival were determined. This study was approved by the Cedars-Sinai Medical Center Institutional Review Board.

Statistical Analysis

Numerical variables that were approximately normally distributed were summarized by mean and standard deviation and were compared across two groups by the independent samples *t* test. Numerical variables that were not approximately normally distributed were summarized by median and interquartile range and were compared across two groups by the Wilcoxon rank-sum test. Categorical variables were summarized by frequency and percent and were compared across groups by the Fisher exact test. Survival was estimated by the Kaplan–Meier method and was compared across groups by the log-rank test. A two-sided 0.05 significance level was used throughout. All statistical calculations were made using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

From January 1, 2000 to December 31, 2011, 516 patients with node positive high-risk tumors were identified (111 HER2+, 182 TNBC, 223 YA) from our database. A total of 299 patients were excluded because the ultimate surgical operation was mastectomy (40 Her2+, 120 TNBC, 139 YA). Sixteen (10 HER2+, 1 TNBC, 5 YA) patients were excluded because the available pathologic data was insufficient. Subsequently, 15 (4 HER2+, 6 TNBC, 5 YA) patients were excluded, because the nodal disease was detected only by IHC. The final analysis included 186 patients with high-risk tumors treated with breast conserving surgery found to have at least one positive node detected by H & E staining: 57 of 186 (31 %) HER2+, 55 of 186 (30 %) TNBC, 74 of 186 (40 %) YA.

Overall, 125 of 186 (67 %) patients would have been eligible for the Z0011 trial; 61 of 186 (33 %) did not meet Z0011 criteria. Reasons for ineligibility were as follows: 35 of 61 (57 %) had clinically positive nodes at presentation, 3 of 61 (5 %) had clinical T3 tumors, 3 of 61 (5 %) had neoadjuvant therapy prior to lumpectomy, 4 of 61 (7 %) had failed intraoperative lymphatic mapping, 2 of 61 (3 %) had evidence of gross extracapsular extension at the time of SNB, 10 of 61 (16 %) had three or more positive SLN, 1 of 61 (2 %) did not have SNB due to pregnancy, 3 of 61 (3 %) had SNB performed with ALND for reasons undetermined. Table 1 lists the reasons for exclusion by subgroup (HER2+, TNBC, and YA). After those with clinically positive nodes were excluded

TABLE 1 Reasons for exclusion from the Z0011 trial by subgroup

Reason for exclusion	HER2+ ($n = 12$)	TNBC ($n = 26$)	Young age ($n = 23$)	Total ($N = 61$)
Clinically positive nodes	3	19	13	35
Clinical T3 tumor	0	2	1	3
Neoadjuvant therapy	2	0	1	3
Failed mapping	1	0	3	4
Three or more +SLN	5	4	1	10
Grossly positive nodes	1	0	1	2
SNB not performed	0	1	3	4

HER2+ HER2-positive, *TNBC* triple-negative breast cancer, *SLN* sentinel lymph node, *SNB* sentinel node biopsy

TABLE 2 Comparison of patient and tumor characteristics between group that met Z0011 eligibility criteria and group that did not meet Z0011 criteria

Characteristic	Did not met Z0011 criteria ($N = 61$)	Met Z0011 criteria ($N = 125$)	p value	Test
Histology, % (n/N)			0.15	Fisher
Ductal	93 (57/61)	86 (107/125)		
Lobular	0 (0/61)	6 (7/125)		
Mixed	7 (4/61)	9 (11/125)		
Tumor grade, % (n/N)			**0.02**	**Fisher**
Low	**2 (1/61)**	**6 (7/124)**		
Intermediate	**18 (11/61)**	**34 (42/124)**		
High	**80 (49/61)**	**61 (75/124)**		
Multifocality, % (n/N)	16 (9/53)	23 (29/124)	0.33	Fisher
Lymphovascular invasion, % (n/N)	59 (31/53)	63 (77/123)	0.62	Fisher
Extranodal extension, % (n/N)	**53 (30/57)**	**29 (35/123)**	**<0.01**	**Fisher**
Tumor size, median (IQR)	**26.5 (18.5–38)**	**21.5 (14.5–29.5)**	**<0.01**	**WRST**
	$N = 60$	**$N = 124$**		
Tumor size, % (n/N)			**0.05**	**Fisher**
<2 cm	**27 (16/60)**	**44 (55/124)**		
2–5 cm	**65 (39/60)**	**51 (63/124)**		
≥5 cm	**8 (5/60)**	**5 (6/124)**		
Ki67, median (IQR)	**40 (22–52)**	**22 (14–39)**	**<0.01**	**WRST**
	$N = 54$	**$N = 117$**		
Ki67 level, % (n/N)			**<0.01**	**Fisher**
Low	**6 (3/54)**	**15 (17/117)**		
Intermediate	**24 (13/54)**	**40 (47/117)**		
High	**70 (38/54)**	**45 (53/117)**		
Age, mean (SD)	54 (15)	48 (12)	0.01	t test

Bold values indicate the results that had a significant p value

IQR interquartile range, *SD* standard deviation, *WRST* Wilcoxon rank-sum test

from the analysis, only 24 of 149 (16 %) would have been considered ineligible and 125 of 149 (84 %) would have been considered eligible.

Comparison of those who met Z0011 eligibility criteria and those who did not identified larger tumor size, higher tumor grade, presence of microscopic ENE, and higher Ki67 to be significantly associated with exclusion from Z0011. Patient age at diagnosis, tumor histology, multifocality, and presence of LVI did not differ significantly between the two groups (Table 2).

HER2 positivity was associated with the lowest rate of ineligibility compared with TNBC and YA (16 vs. 53 and 31 %, respectively, $p < 0.001$). Three patients in the HER2+ group were considered ineligible, because they presented with clinically positive nodes. Other reasons for ineligibility within this group included neoadjuvant therapy ($n = 2$), failed intraoperative lymphatic mapping ($n = 1$), 3 or more positive SLNs ($n = 5$), and gross extracapsular extension at the time of SNB ($n = 1$). The large majority of patients with HER2+ breast cancer that presented with clinically positive nodes elected to have mastectomy. The highest rate of ineligibility was found among patients with TNBC (53 %). Nineteen cases were deemed ineligible because of clinically involved nodes at presentation and two had clinical T3 tumors. After examining only clinical T1-2N0 cases, 33 of 39 (85 %) patients with TNBC would have been eligible for the Z0011 trial. The other reasons for ineligibility within this subgroup included three or more positive SLNs ($n = 4$) and one patient was pregnant at the time of her operation, so SNB was not performed. Thirteen YA cases presented with clinically positive nodes and one had a clinical T3 tumor. After examining only clinical T1-2N0 YA cases 48 of 60 (80 %) would have been eligible for the Z0011 trial. The other reasons for ineligibility within this subgroup included one with neoadjuvant therapy, six did not have SNB (3 failed mapping, 3 for reasons unknown), one had three or more positive SLNs, and one had grossly positive nodes at the time of operation.

Among those who were eligible for Z0011, 105 of 125 (84 %) had ALND and 20 of 125 (16 %) did not have ALND. Of those who had ALND, 48 of 125 (38 %) had involvement of non-SLN (NSLN), and the median number of NSLNs involved was one (range 1–3). With median follow-up of 5.5 years, survival was similar between those who had ALND and those who did not ($p = 0.94$). There were no regional recurrences in either group.

DISCUSSION

The ACOSOG Z0011 trial revealed no difference in survival for patients with clinical T1-2N0 invasive breast cancer with 1–2 positive SLNs with or without ALND. The results of the trial led to significant changes in the practice guidelines for patients with SLN-positive early breast cancer.[3,4] The initial report of the results in 2010 was met with considerable uncertainty from various oncologic specialties.[5–14] One of the areas of controversy surround the relevance of the Z0011 trial in patients with high-risk breast cancer, including those with ER-negative and HER2+ cancer and diagnosis at a young age. HER2 testing was not routinely performed or reported during the accrual period for the ACOSOG Z0011 trial; therefore, it is unclear how many patients in the trial had Her2+ breast cancer. The proportion of study participants younger than age 50 years was 38 and 16 % had ER-negative tumors.[1,2] Despite this, it has been argued that patients in these high-risk categories were underrepresented in the ACOSOG Z0011 trial and that the conclusions from the trial should not apply to these subsets of patients.[6,8–10]

This study evaluates the rate of ineligibility for the ACOSOG Z0011 trial among patients with high-risk breast cancer undergoing BCT who had at least one positive lymph node detected by H & E staining. After applying the trial eligibility requirements to this group of patients, nearly 70 % of node-positive high-risk breast cancer was found to be eligible for the Z0011 trial. The most common reason for ineligibility was clinically positive nodes. After examining only patients with clinically negative nodes, as defined in the eligibility criteria of the Z0011 protocol, up to 85 % of cases would have been eligible for the Z0011 trial. The highest rate of ineligibility was found among patients with TNBC (53 %). However, after examining only clinical T1-2N0 cases in this cohort, 33 of 39 (85 %) patients with TNBC would have been eligible for the Z0011 trial.

Yi and colleagues evaluated the applicability of the Z0011 trial results to their population of patients with clinical T1-2N0 breast cancer and 1–2 positive SLNs.[15] They found that 75 % of patients were eligible for the trial and could have avoided ALND. The most common reason for Z0011 ineligibility in their study was presence of three or more positive SLNs. Only 12.5 % of patients in this study had ER-negative tumors. The investigators did not report data on HER2-positivity or how many patients were younger than age 50 years.

Dengel et al. conducted a prospective series of consecutive patients with a positive SLN treated with BCT.[16] They found that 84 % of their patients qualified for the Z0011 trial. Their analysis did not include node-positive patients who did not have SLNB, whereas the current analysis began with an evaluation of all node-positive patients, resulting in a higher proportion of patients who would have been ineligible due to clinically palpable nodes. However, after those with clinically positive nodes were excluded in our study, we found that a similar proportion (85 %) of patients would have been eligible to avoid ALND. The most common reason for trial ineligibility in the Dengel study was the number of patients with SLN disease detected by IHC only. The investigators did not find age, hormone receptor status, or HER2 status to be significant predictors of requiring ALND. Only 11 % ($n = 18$) of the patients in their study had HER2+ tumors, 23 % ($n = 29$) had ER-negative tumors, and median patient age was 58 years. Our study included 57 patients with HER2+ tumors, 55 patients with TNBC, and 74 with ER+/HER2- tumors diagnosed before age 50 years.

Patients who fell into the ineligible category in our study had larger tumor size, higher tumor grade, more microscopic ENE, and higher Ki67. Yi and colleagues found that younger age, larger tumor size, higher volume of disease in the SLN, and ENE were associated with trial ineligibility, and patients with these tumor characteristics were more likely to have ALND.[15] Dengel et al. found that larger tumor size was the only one of these tumor factors associated with completion ALND and exclusion from Z0011.[16] These various tumor characteristics may contribute to NSN involvement and have been included in several nomograms used to predict likelihood of NSN metastases in patients with a positive SLN.[17–21] However, these models cannot identify a subset of SLN-positive patients without risk of additional NSN disease, demonstrating the limitations of predictive models and using tumor characteristics to predict presence of NSN metastases.

The majority of patients with a positive SLN had completion ALND in our study. Thirty-eight percent of these high-risk patients had NSN disease, and the median number of involved NSN was one. The incidence of NSN metastases in most studies of SNB with ALND ranges from 37 to 45.5 %.[22–25] In the Z0011 trial, 27 % in the ALND group had NSN involvement.[1,2] Our reported incidence of NSN involvement was similar to that of the populations included in these studies, indicating that the high-risk populations do not have a higher incidence of NSN involvement than lower-risk populations. Although the number of patients who did not have completion ALND in this group was small, their survival did not differ significantly compared with those who had ALND and there were no regional recurrences, further corroborating the case that ALND can be avoided safely in these high-risk patients.

In conclusion, the ACOSOG Z0011 trial eligibility criteria apply to a significant proportion of patients with HER2+ tumors, TNBC, and young age at diagnosis. This

study of the survival of a small group of high-risk breast cancer patients further corroborates the survival data of ACOSOG Z0011 and suggests that ALND can be avoided in approximately 70 % of patients with node-positive, high-risk breast cancer and 85 % of SLN-positive patients with clinically negative axillary lymph nodes undergoing breast conserving surgery.

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