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CLINICAL TRIAL

Retrospectively validating the results of the ACOSOG Z0011 trial in a large Asian Z0011-eligible cohort

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Abstract

Purpose The Z0011 trial demonstrated that axillary dissection (ALND) could be omitted during breast-conserving therapy for cT1-2N0 breast cancers with 1–2 metastatic SLNs. However, that result has not been validated in a larger cohort and the significance of the small number of SLNs remains unclear. This study aimed to validate the Z0011 results within an Asian Z0011-eligible cohort and determine whether the number of sentinel lymph nodes (SLNs) influenced the Z0011-based outcomes.

Methods Data from Asian patients who fulfilled the Z0011 criteria were collected from five hospitals. Disease recurrence (DR) was compared between patients who underwent ALND or SLN dissection (SLND) alone. Propensity-score matching was performed to reduce the effects of potential selection biases.

Results During 2010–2016, 1750 Asian patients had 1–2 SLN metastases and fulfilled the Z0011 criteria. These patients included 707 cases treated using SLND alone (40%) and 967 patients with ≤ 2 SLNs (55%). Ninety-five patients (5.4%) experienced DR at a median interval of 50 months, although the rates of DR were similar in the ALND and SLND groups. The adjusted hazard ratios for DR after ALND omission were 0.95 (95% CI 0.55–1.64) among the entire cohort and 0.83 (95% CI 0.34–2.03) among patients with ≤ 2 SLNs.

Conclusions In this Asian Z0011-eligible cohort, ALND omission did not increase risk of DR, even among patients with ≤ 2 SLNs. Therefore, the Z0011 strategy might be safely applied in Asia, and a small number of SLNs did not significantly influence this strategy.

Keywords Axillary lymph node dissection · Breast cancer · Sentinel lymph node biopsy

Introduction

Axillary management of breast cancer has evolved based on the development of adjuvant therapies, which range from less extensive treatments to conventional axillary lymph node dissection (ALND). The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that clinically node-negative women with T1–T2 invasive breast cancer experienced excellent local control and survival (based on a median follow-up of 6.4 years) after sentinel lymph node dissection (SLND) without ALND, as part of breast-conserving surgery (BCT) with whole-breast irradiation, even if metastases were present in 1–2 sentinel lymph nodes (SLNs) [1]. The long-term follow-up data from the Z0011 study also revealed that the 10-year overall survival (OS) and disease-free survival (DFS) rates for patients who underwent SLND alone were not inferior to those for patients who underwent ALND [2]. Furthermore, SLND alone provided excellent loco-regional control based on early and late recurrence rates [3, 4].

The Z0011 results have led to a change in the standard axillary management of breast cancer [5–7]. However, the

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Z0011 study was closed early because of the excellent outcomes, and subanalyses were not completed for various conditions. Furthermore, the Z0011 results have not been validated in a larger cohort with a balance of patients who did or did not undergo ALND. Moreover, the studies that have validated the utility of the Z0011 strategy were performed using mostly Western populations [8–11]. Thus, as breast cancers in Asian women exhibit substantially different characteristics from those in Western patients [12], the feasibility of the Z0011 strategy in the Asian population remains unclear. In addition, no studies have evaluated potential confounding that could be attributed to the total number of SLNs in the Z0011 study, which omitted ALND based on the presence of 1–2 metastatic SLNs, regardless of pathological confirmation when the patient had 1–2 SLNs. Caution must be exercised when applying the Z0011 strategy to those patients, as a small number of total SLNs does not guarantee a lower metastatic burden in the axillary nodes. Therefore, the present study aimed to validate the Z0011 results within a large Z0011-eligible cohort of Asian patients. As a secondary aim, this study also aimed to investigate whether ALND omission among Z0011-eligible patients with ≤ 2 SLNs was associated with poorer outcomes.

Methods

Selection of the Z0011-eligible cohort

This retrospective study evaluated data from breast cancer databases that were prospectively maintained by five Korean teaching hospitals: Asan Medical Center, National Cancer Center, Samsung Medical Center, Seoul National University Hospital, and Severance Hospital. From these databases, we selected Z0011-eligible patients who were treated during 2010–2016 and fulfilled the eligibility criteria of the ACOSOG Z0011 trial. In general, these women had T1–T2 clinically node-negative invasive breast cancer, had undergone BCT, and had 1–2 positive SLNs based on routine hematoxylin and eosin staining; the detailed inclusion and exclusion criteria were the same as those for the ACOSOG Z0011 trial [1]. The Z0011-eligible Asian patients were subdivided according to whether the patients underwent SLND alone (the "SLND alone" group) or conventional ALND after SLND (the "ALND" group). The ALND procedure was defined as anatomical level I and II dissection that included ≥ 10 nodes. The SLNs were defined as the lymph nodes (LNs) that were identified using a blue dye and/or radioactive tracer. Whole-breast radiation therapy (RT) was planned for all women, and adjuvant systemic therapy had been selected by the physician and patient while being mindful of the ACOSOG Z0011 trial results.

Study end-point

The primary end-point was defined as disease recurrence, which included all types of recurrence (local, regional, and distant recurrence). Patients were followed via their medical records until October 2017 to identify any disease recurrence. The interval to recurrence was measured from the time of surgery to the first development of loco-regional or distant recurrence. Patients without confirmed recurrence at the time of analysis were censored at the date of their last follow-up.

Statistical analyses

The two groups' categorical and continuous characteristics were compared using the Chi square test and two-sample *t*-test. Survival curves were compared using the Kaplan–Meier method and log-rank test. Cox's proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) in order to assess the univariable and multivariable associations of recurrence with the prognostic variables and treatments.

Propensity score (PS)-matched analyses were performed to reduce possible selection biases. The PSs were calculated using a logistic regression model with omission of ALND as a dependent variable, and other independent variables were selected based on their potential association with ALND omission via univariable analyses. The cases (SLND alone group) and controls (ALND group) were paired 1:1 based on these PSs using the nearest-neighbor matching method. Standardized differences were estimated before and after the matching to evaluate the balance of the covariates, with small absolute values of < 0.1 considered indicative of balance between the cohorts [13, 14]. All statistical tests were two-sided and a *P*-value of ≤ 0.05 was considered statistically significant. The analyses were performed using IBM SPSS software (version 20.0; IBM Corp., Armonk, NY, USA) and SAS software (version 9.3; SAS Institute, Cary, NC, USA).

Results

Characteristics of the Asian Z0011-eligible cohort

Between January 2010 and December 2016, 1,750 Asian patients fulfilled the Z0011 eligibility criteria, had undergone BCT, and had 1–2 SLN metastases. The baseline characteristics of the Asian Z0011-eligible cohort are summarized in Table 1. The median age was 49 years, the median tumor size was 2.1 cm, and 83.4% of the patients

Table 1 Baseline characteristics of the Z0011-eligible patients

	Total No. (%)	SLND alone No. (%)	ALND No. (%)	ALND omission (%)	*P* value
Subject number	1750	707	990	40.4	
Patient age, years (range)	49 (25–92)	50 (25–88)	50 (25–88)		0.426
≤ 50	982 (56.1)	399 (56.4)	553 (55.9)	40.6	
> 50	768 (43.9)	308 (43.6)	437 (44.1)	40.1	
BMI, mean (Kg/m^2)	24.8	23.3	26.0		0.003
≤ 23.0	817 (46.7)	360 (50.9)	435 (43.9)	44.1	
> 23.0	933 (53.3)	347 (49.1)	555 (56.1)	37.2	
Tumor size, mean (cm)	2.1	2.0	2.2		< 0.001
T category					< 0.001
T1	983 (56.2)	447 (63.2)	502 (50.7)	45.5	
T2	767 (43.8)	260 (36.8)	488 (49.3)	33.9	
N category					< 0.001
N1mi	229 (13.0)	184 (26.0)	42 (4.2)	80.6	
N1	1393 (79.6)	520 (73.6)	824 (83.2)	34.4[a]	
N2	114 (6.5)	3 (0.4)	110 (11.1)		
N3	14 (0.8)		14 (1.4)		
No. of positive SLN(s)					< 0.001
1	1458 (83.3)	646 (91.4)	763 (77.1)	44.3	
2	292 (16.7)	61 (8.6)	227 (22.9)	20.9	
No. of total SLNs, mean	2.9	3.2	2.7		< 0.001
Total SLNs ≥ 3	783 (44.7)	353 (50.0)	420 (42.4)	45.1	
Total SLNs ≤ 2	967 (55.3)	354 (50.0)	570 (57.6)	36.6	
Axillary sonographic finding					0.015
Normal	1586 (90.7)	657 (92.9)	884 (89.4)	41.4	
Suspicious	163 (9.3)	50 (7.1)	105 (10.6)	30.7	
Missing	1	0	1		
Histologic grade					0.013
1	223 (12.8)	112 (16.0)	111 (11.3)	50.2	
2	986 (56.8)	401 (57.2)	552 (56.2)	40.7	
3	527 (30.4)	188 (26.8)	319 (32.5)	35.7	
Missing	14	6	8		
Ki-67					0.149
≤ 20%	1268 (72.6)	537 (76.1)	708 (71.6)		
> 20%	479 (27.4)	169 (23.9)	281 (28.4)		
Missing	3	1	1		
Lymphovascular invasion					0.022
Present	818 (47.0)	301 (42.9)	490 (49.6)		
Absent	924 (53.0)	401 (57.1)	497 (50.4)		
Missing	8	5	3		
ER status					0.031
Positive	1459 (83.4)	606 (85.7)	814 (82.2)		
Negative	291 (16.6)	101 (14.3)	176 (17.8)		
PR status					0.005
Positive	1303 (74.5)	552 (78.1)	718 (72.5)		
Negative	447 (25.5)	155 (21.9)	272 (27.5)		
HER2 status					0.037
Positive	281 (16.2)	108 (15.3)	167 (17.1)		
Negative	1453 (83.8)	597 (84.7)	809 (82.9)		
Missing	16	2	14		

Table 1 (continued)

	Total No. (%)	SLND alone No. (%)	ALND No. (%)	ALND omission (%)	*P* value
Molecular subtype					
Luminal	1459 (84.1)	606 (86.0)	814 (83.4)		
ER+, HER2−	1278 (73.7)	539 (76.5)	705 (72.2)		
ER+, HER2+	166 (9.6)	66 (9.4)	95 (9.7)		
HER2	115 (6.6)	42 (6.0)	72 (7.4)		
Triple negative	175 (10.1)	58 (8.2)	104 (10.7)		
Missing	16	2	14		
Histologic type					0.170
IDC	1611 (92.1)	644 (91.1)	916 (92.5)		
ILC	67 (3.8)	37 (5.2)	29 (2.9)		
IDC and ILC	25 (1.4)	7 (1.0)	18 (1.8)		
Others	47 (2.7)	19 (2.7)	27 (2.7)		
Adjuvant therapy					
Chemotherapy	1525 (87.1)	578 (81.8)	896 (90.5)		< 0.001
Radiation therapy	1682 (96.1)	681 (96.3)	948 (95.8)		0.656
Endocrine therapy	1461 (83.5)	601 (85.0)	823 (83.1)		0.528
Median follow-up, months (IQR)	50 (31–63)	40 (26–57)	56 (36–67)		
Recurrence, total	95 (5.4)	24 (3.4)	66 (6.7)		
Axilla	7 (0.4)	2 (0.3)	4 (0.4)		
Ipsilateral breast	22 (1.3)	6 (0.8)	14 (1.4)		
Distant organ	66 (3.8)	16 (2.3)	48 (4.8)		

ALND axillary lymph node dissection, *BMI* body mass index, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *PR* progesterone receptor, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection

[a]The proportion of ALND omission was calculated from all patients with macrometastases (N1–3 categories) as a whole

had estrogen receptor (ER)-positive cancers. The adjuvant treatments were chemotherapy (87.1% of patients) and RT (96.1% of patients), with endocrine therapy provided for all ER-positive cancers and for ER-negative but progesterone receptor (PR)-positive cancers. The median follow-up period was 50 months (range 7–84 months).

The cohort was subdivided into 990 patients (57%) who had undergone ALND and 707 patients (40%) who underwent SLND alone. Fifty-three patients (3%) were excluded from the analyses because they had undergone SLND plus ALND but the extent of the dissection was confined to level I. There was no incremental increase in the ALND omission rate according to the year (2010–2016) in which the patients were treated. Although they were selected based on the Z0011 criteria, the Asian Z0011-eligible cohort had slightly different clinical and tumor characteristics. For example, the patients from the Asian Z0011-eligible cohort were younger, had larger and higher-grade tumors, and exhibited more frequent lymphovascular invasion than the original Z0011 participants (Supplementary Table S1). Among the 1750 Asian Z0011-eligible patients, 967 patients (55%) had ≤ 2 SLNs removed via SLND, although the characteristics of this sub-cohort were not different from those of the entire cohort (Table 2).

Characteristics of the SLND alone group from the Asian Z0011-eligible cohort

Among the Asian Z0011-eligible cohort, the 707 patients in the SLND alone group had smaller and lower-grade tumors than the ALND group. However, the SLND alone group still had larger and higher-grade tumors than the original Z0011 cohort (Supplementary Table S1). Omission of ALND was more common for patients with T1 tumors than patients with T2 tumors (45.5% vs. 33.9%; $P < 0.001$) and for lower-grade tumors than higher-grade tumors (histological grade 1: 50.2%, grade 2: 40.7%, grade 3: 35.7%; $P < 0.001$). Omission of ALND was also more common for patients with 1 SLN metastasis than 2 SLN metastases (44.3% vs. 20.9%; $P < 0.001$), for micro-metastasis than macro-metastasis (80.6% vs. 34.4%; $P < 0.001$), and for > 2 total SLNs than ≤ 2 total SLNs (45.1% vs. 36.6%; $P < 0.001$) (Table 1). Obesity and preoperative axillary sonographic findings might also affect surgeons' decision to omit ALND. Omission

Table 2 Baseline characteristics of the patients who had 2 or less sentinel lymph nodes

	Total No. (%)	SLND alone No. (%)	ALND No. (%)	ALND omission (%)	*P*-value
Subject number	967	354	570	36.6	
Patient age, years	51 (27–88)	51 (29–82)	51 (27–88)		0.946
≤ 50	530 (54.8)	193 (54.5)	313 (54.9)	36.4	
> 50	437 (45.2)	161 (45.5)	257 (45.1)	36.8	
BMI, average (Kg/m^2)	26.0	23.3	27.7		0.017
≤ 23.0	434 (44.9)	177 (50.0)	239 (41.9)	40.8	
> 23.0	533 (55.1)	177 (50.0)	331 (58.1)	33.2	
Tumor size, mean (cm)	2.1	2.0	2.2		< 0.001
T category					< 0.001
T1	534 (55.2)	225 (63.6)	280 (49.1)	42.1	
T2	433 (44.8)	129 (36.4)	290 (50.9)	29.8	
N category					< 0.001
N1mi	156 (16.1)	124 (35.0)	29 (5.1)	79.5	
N1	730 (75.5)	229 (64.7)	462 (81.1)	28.4[a]	
N2	68 (7.0)	1 (0.3)	66 (11.6)		
N3	13 (1.3)		13 (2.3)		
Number of positive SLN(s)					< 0.001
1	868 (89.8)	339 (95.8)	489 (85.8)	39.1	
2	99 (10.2)	15 (4.2)	81 (14.2)	15.2	
Axillay sonographic finding					0.852
Normal	912 (94.4)	335 (94.6)	541 (95.1)	36.7	
Suspicious	54 (5.6)	19 (5.4)	28 (4.9)	35.2	
Missing	1		1		
Histologic grade					0.005
1	122 (12.7)	57 (16.2)	65 (11.4)	46.7	
2	559 (59.0)	211 (60.1)	321 (56.4)	37.7	
3	282 (29.3)	83 (23.6)	183 (32.2)	29.4	
Missing	4	3	1		
Ki-67					0.092
≤ 20%	648 (67.1)	251 (71.1)	377 (66.1)		
> 20%	318 (32.9)	102 (28.9)	193 (33.9)		
Missing	1	1			
Lymphovascular invasion					0.022
Present	498 (51.6)	162 (46.0)	31 (54.9)		
Absent	467 (48.4)	190 (54.0)	257 (45.1)		
Missing	2	2			
ER status					0.176
Positive	801 (82.8)	302 (85.3)	466 (81.8)		
Negative	106 (11.0)	52 (14.7)	104 (18.2)		
PR status					0.072
Positive	723 (74.8)	278 (78.5)	417 (73.2)		
Negative	244 (25.2)	76 (21.6)	153 (26.8)		
HER2 status					0.655
Positive	160 (16.5)	56 (15.8)	99 (17.4)		
Negative	795 (82.2)	297 (83.9)	460 (80.7)		
Missing	12	1	11		
Molecular subtype					
Luminal	789 (81.6)	301 (85.0)	455 (79.8)		
ER+, HER2−	702 (72.6)	269 (76.0)	404 (70.9)		
ER+, HER2+	87 (9.0)	32 (9.0)	51 (8.9)		

Table 2 (continued)

	Total No. (%)	SLND alone No. (%)	ALND No. (%)	ALND omission (%)	*P*-value
HER2	73 (7.5)	24 (6.8)	48 (8.4)		
Triple negative	93 (9.6)	28 (7.9)	56 (9.8)		
Missing	12	1	11		
Histologic type					0.089
IDC	893 (92.3)	321 (90.7)	530 (93.0)		
ILC	38 (3.9)	20 (5.6)	17 (3.0)		
IDC and ILC	8 (0.8)	1 (0.3)	7 (1.2)		
Others	28 (2.9)	12 (3.4)	16 (2.8)		
Adjuvant treatment					
Chemotherapy	826 (85.4)	283 (79.9)	501 (87.9)		0.002
Radiation therapy	928 (96.0)	340 (96.0)	545 (95.6)		0.907
Endocrine therapy	802 (82.9)	301 (85.0)	469 (82.3)		0.622
Median follow-up, months (IQR)	52 (32–64)	40 (26–58)	57 (36–68)		
Recurrence, total	53 (5.5)	9 (2.5)	40 (7.0)		
Axilla	1 (0.1)	1 (0.3)	0 (0.0)		
Ipsilateral breast	12 (1.2)	1 (0.3)	9 (1.6)		
Distant organ	40 (4.1)	7 (2.0)	31 (5.5)		

ALND axillary lymph node dissection, *BMI* body mass index, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *PR* progesterone receptor, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection

[a]The proportion of ALND omission was calculated from all patients with macrometastases (N1–3 categories) as a whole

of ALND was more common for patients with a BMI of ≤ 23 kg/m^2 than a BMI of > 23 kg/m^2 (44.1% vs. 37.2%; $P = 0.014$) and for patients with no suspicious nodes on preoperative axillary sonography than patients with suspicious nodes (47.3% vs. 26.4%; $P < 0.001$).

Based on the policy of the Korean National Health Insurance Service, hormone receptor status and human epidermal growth factor receptor 2 (HER2) gene expression status are not usually determined before surgical treatment of breast cancer. Therefore, these factors were not considered as potentially affecting the decision to omit ALND.

Outcomes in the Asian Z0011-eligible cohort

Among the 1750 patients, 95 patients (5.4%) experienced disease recurrence during a median follow-up period of 50 months, including 24 patients (3.4%) in the SLND alone group, 66 patients (6.7%) in the ALND group, and 5 patients who had been excluded because of incomplete ALND. Among the entire Asian Z0011-eligible cohort, the recurrences included 29 cases (1.7%) of loco-regional recurrence (LRR) and 66 cases (3.8%) of distant recurrence. Among the 29 LRRs, 8 cases (1.1%) occurred in the SLND alone group and 18 cases (1.8%) occurred in the ALND group. Among the 66 distant recurrences, 15 cases (2.3%) occurred in the SLND alone group and 48 cases (4.8%) occurred in the ALND group (Table 1). The median follow-up periods were 40 months for the SLND alone group and 56 months for the ALND group. The original Z0011 study revealed 5-year cumulative LRR incidences of 3.3% in the SLND alone group and 4.0% in the ALND group [4], which were comparable to our incidences of LRR despite the noticeably poorer tumor characteristics in the present study.

Disease recurrence in the SLND alone group was not significantly different from that in the ALND group (unadjusted HR 0.672, 95% CI 0.420–1.076; Fig. 1a). In the univariable analyses, significant differences in disease recurrence were observed according to T category, histological grade, lymphovascular invasion, Ki-67 expression, ER status, PR status, and RT treatment. No significant difference in recurrence was observed according to the number (1 vs. 2) or size (micro vs. macro) of metastatic SLNs, despite the noticeably different rates of ALND omission in those subgroups. Furthermore, ALND omission did not significantly influence disease recurrence in a model that included T category (T1 vs. T2), histological grade (1–2 vs. 3), lymphovascular invasion (absent vs. present), Ki-67 expression ($> 20\%$ vs. $\leq 20\%$), ER status (negative vs. positive), PR status (negative vs. positive), and RT treatment (no vs. yes). In that model, patients who did not undergo ALND had an adjusted HR for disease recurrence of 0.848 (95% CI 0.525–1.370). The multivariable analyses revealed that recurrence was significantly influenced by T category, lymphovascular invasion, Ki-67 expression, and RT treatment. Histologic grade was highly

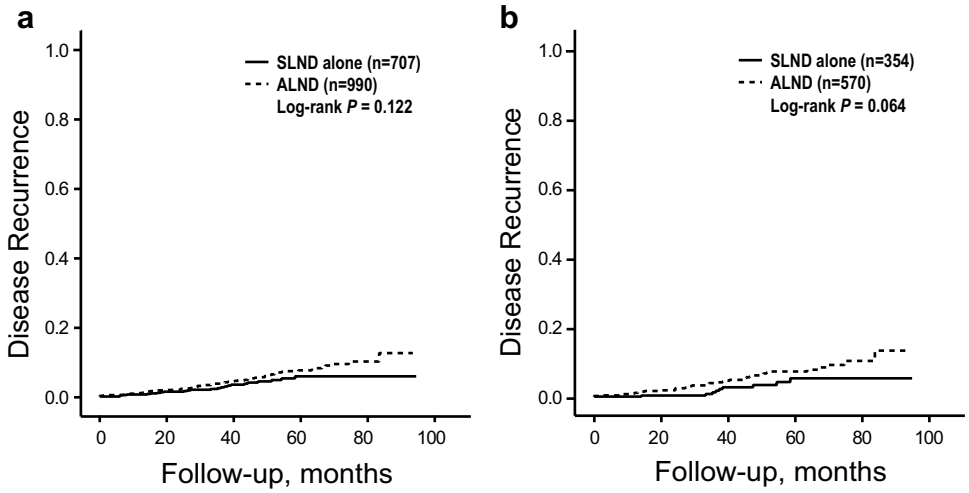

Fig. 1 Cumulative incidence of disease recurrence by type of axillary surgery in **a** the entire Z0011-eligible patients; **b** the patients who had ≤ 2 sentinel lymph nodes *ALND* axillary lymph node dissection, *SLND* sentinel lymph node dissection, *OS* overall survival

correlated with the presence of lymphovascular invasion and Ki-67 expression level. Additionally, ER and PR status were correlated with T category. There might be confounding effects between those variables arising from a specific biologic feature of tumor. ER, PR status and histologic grade were not significant risk factors for disease recurrence in the model for multivariable analyses (Table 3). We also performed subgroup analyses according to hospital, age, BMI, T category, histological grade, ER status, PR status, HER2 gene expression status, Ki-67 expression, lymphovascular invasion, preoperative axillary sonographic finding, and adjuvant therapy. Omission of ALND did not increase the risk of disease recurrence within any of these subgroups (Supplementary Table S2).

The SLND alone and ALND groups were also compared among the 967 Z0011-eligible Asian patients with ≤ 2 SLNs. In those analyses, ALND omission did not significantly influence disease recurrence in the univariable analysis (unadjusted HR 0.489, 95% CI 0.236–1.011; Fig. 1b) or in the multivariable analysis (adjusted HR 0.605, 95% CI 0.289–1.269). However, the multivariable analyses confirmed that disease recurrence was significantly influenced by T category, Ki-67 expression, and RT treatment. Similar to the main analyses, ER, PR status, histologic grade, and lymphovascular invasion were not significant risk factors for disease recurrence in that model (Table 4). Subgroup analyses of the 967 patients with ≤ 2 SLNs revealed that ALND omission did not increase the risk of disease recurrence in any of the subgroups (Supplementary Table S3).

Comparison of disease recurrence after PS matching

Given that some patient and tumor characteristics could influence the decision to omit ALND, we performed PS matching to reduce selection biases. Among the 1750 Z0011-eligible patients, 111 patients were excluded based on missing data regarding the matching variables, and PS matching was performed for the remaining 1639 patients (687 patients in the SLND alone group and 952 patients in the ALND group). The PSs were calculated using a logistic regression model with ALND omission as the dependent variable and the following independent variables: hospital, age (≤ 50 years, > 50 years), obesity (≤ 23.0 kg/m^2, > 23.0 kg/m^2), T category, number of positive SLNs, histological type, histological grade, ER status, PR status, HER2 gene expression status, Ki-67 expression (≤ 20%, > 20%), lymphovascular invasion, preoperative axillary sonographic findings (normal, suspicious), and RT treatment. After excluding 397 unmatched patients, we identified 1242 PS-matched patients (621 patients in the SLND alone group, 621 patients in the ALND group). Similarly, we identified 660 PS-matched patients (330 patients in the SLND alone group, 330 patients in the ALND group) among the 895 Z0011-eligible patients with ≤ 2 SLNs. The standardized differences before and after the PS matching are summarized in Supplementary Tables S4 and S5.

Among the 1,242 overall PS-matched patients, the adjusted HR for disease recurrence after ALND omission was 0.949 (95% CI 0.550–1.639). Among the 660 PS-matched patients with ≤ 2 SLNs, the adjusted HR for disease recurrence after ALND omission was 0.833 (95% CI 0.342–2.029). These results agreed with our findings from the multivariable analyses and support a broader applicability of the Z0011 result to patients in whom SLND only detects a small number of SLNs. The adjusted HRs after PS matching are shown in Fig. 2, with the reported HR for LRR from the ACOSOG Z0011 trial [4].

Discussion

The present study retrospectively validated the safety of ALND omission in a large Asian Z0011-eligible cohort and evaluated whether the Z0011 strategy was feasible

Table 3 Multivariable analysis for disease recurrence among the entire Z0011-eligible patients

Variable	Univariable analysis		Multivariable analysis[a]	
	HR	*P*-value	HR (95% CI)	*P*-value
Extent of axillary clearance				
ALND	1.00 [Reference]		1.00 [Reference]	
SLND alone	0.672 (0.420–1.076)	0.098	0.848 (0.525–1.370)	0.501
No. of metastatic SLN(s)				
1	1.00 [Reference]			
2	1.137 (0.671–1.928)	0.633		
Size of metastatic SLN(s)				
Micro-	1.00 [Reference]			
Macro-	1.648 (0.797–3.408)	0.178		
T category				
T1	1.00 [Reference]		1.00 [Reference]	
T2	2.773 (1.774–4.332)	< 0.001*	2.172 (1.361–3.467)	0.001*
Histologic grade				
1, 2	1.00 [Reference]		1.00 [Reference]	
3	2.153 (1.416–3.274)	< 0.001*	1.235 (0.760–2.007)	0.393
Lymphovascular invasion				
Absent	1.00 [Reference]		1.00 [Reference]	
Present	2.117 (1.364–3.287)	0.001*	1.667 (1.051–2.645)	0.030*
Ki-67				
≤ 20%	1.00 [Reference]		1.00 [Reference]	
> 20%	2.350 (1.541–3.584)	< 0.001*	1.618 (1.026–2.554)	0.039*
ER status				
Negative	1.00 [Reference]		1.00 [Reference]	
Positive	0.496 (0.313–0.787)	0.003*	1.008 (0.482–2.110)	0.982
PR status				
Negative	1.00 [Reference]		1.00 [Reference]	
Positive	0.515 (0.336–0.789)	0.002*	0.635 (0.330–1.220)	0.173
HER2 status				
Negative	1.00 [Reference]			
Positive	0.700 (0.362–1.353)	0.289		
Adjuvant chemotherapy				
Yes	1.00 [Reference]			
No	1.366 (0.742–2.515)	0.316		
Adjuvant radiotherapy				
Yes	1.00 [Reference]		1.00 [Reference]	
No	8.813 (5.123–15.163)	< 0.001*	6.408 (3.679–11.161)	< 0.001*

ALND axillary lymph node dissection, *CI* confidence interval, *ER* estrogen receptor, *HR* hazard ratio, *PR* progesterone receptor, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection

[a]Variables which have *P*-values < 0.1 in univariable analyses were inputted into multivariable analysis

*P-value < 0.05

for patients with ≤ 2 SLNs. The relatively low proportion of ALND omission in the present cohort (40% among all patients) reflects an incomplete validation of the Z0011 result within a non-Western population, although that paradoxically facilitated a balanced study to compare ALND and no ALND. Relative to the Z0011 participants, the Asian Z0011-eligible patients had larger and higher-grade tumors and more frequent lymphovascular invasion, which may reflect racial differences between Asian and Western women. In this context, the characteristics of Asian Z0011-eligible patients have not been comprehensively evaluated, as previous studies involving Asian women have been limited by their small sample or non-omission of ALND [15, 16]. A recent Japanese study has also evaluated Japanese Z0011-eligible women and revealed, similar to the present study, that they had larger tumors and more

Table 4 Multivariable analysis for disease recurrence among the patients who had ≤ 2 sentinel lymph nodes

Variable	Univariable analysis		Multivariable analysis[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Extent of axillary clearance				
ALND	1.00 [Reference]		1.00 [Reference]	
SLND alone	0.489 (0.236–1.011)	0.052	0.605 (0.289–1.269)	0.184
No. of metastatic SLN(s)				
1	1.00 [Reference]			
2	1.205 (0.513–2.831)	0.666		
Size of metastatic SLN(s)				
Micro-	1.00 [Reference]			
Macro-	1.725 (0.683–4.359)	0.251		
T category				
T1	1.00 [Reference]		1.00 [Reference]	
T2	3.395 (1.800-6.402)	< 0.001*	2.542 (1.306–4.947)	0.006*
Histologic grade				
1, 2	1.00 [Reference]		1.00 [Reference]	
3	2.556 (1.448–4.511)	0.001*	1.403 (0.722–2.729)	0.318
Lymphovascular invasion				
Absent	1.00 [Reference]		1.00 [Reference]	
Present	1.707 (0.948–3.076)	0.073	1.188 (0.634–2.228)	0.590
Ki-67				
≤ 20%	1.00 [Reference]		1.00 [Reference]	
> 20%	2.732 (1.543–4.836)	0.001*	2.042 (1.098–3.799)	0.024*
ER status				
Negative	1.00 [Reference]		1.00 [Reference]	
Positive	0.563 (0.299–1.063)	0.076	1.107 (0.376–3.261)	0.854
PR status				
Negative	1.00 [Reference]		1.00 [Reference]	
Positive	0.558 (0.310–1.007)	0.052	0.730 (0.273–1.949)	0.530
HER2 status				
Negative	1.00 [Reference]			
Positive	0.645 (0.255–1.629)	0.356		
Adjuvant chemotherapy				
Yes	1.00 [Reference]			
No	1.650 (0.798–3.414)	0.177		
Adjuvant radiotherapy				
Yes	1.00 [Reference]		1.00 [Reference]	
No	5.409 (2.297–12.736)	< 0.001*	3.601 (1.509–9.595)	0.004*

ALND axillary lymph node dissection, *CI* confidence interval, *ER* estrogen receptor, *HR* hazard ratio, *PR* progesterone receptor, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection

[a]Variables which have *P*-values < 0.1 in univariable analyses were inputted into multivariable analysis

*P-value < 0.05

frequent lymphovascular invasion than the Z0011 participants [15]. In contrast, validation studies that involved Western women have revealed tumor characteristics that were at least somewhat different from our findings [5, 11, 17]. Nevertheless, ours is the largest study to validate the Z0011 results among Asian women, and also provided a relatively balanced cohort of patients who did and did not undergo ALND.

The differences in tumor characteristics between the original Z0011 cohort and our Z0011-eligible cohort could be related to unexpected treatment selection based on preoperative axillary evaluations. For example, our cohort involved patients who routinely underwent axillary sonography, and this procedure might have allowed clinically node-negative patients to undergo upfront ALND or neoadjuvant systemic therapy, which would have resulted in these cases being

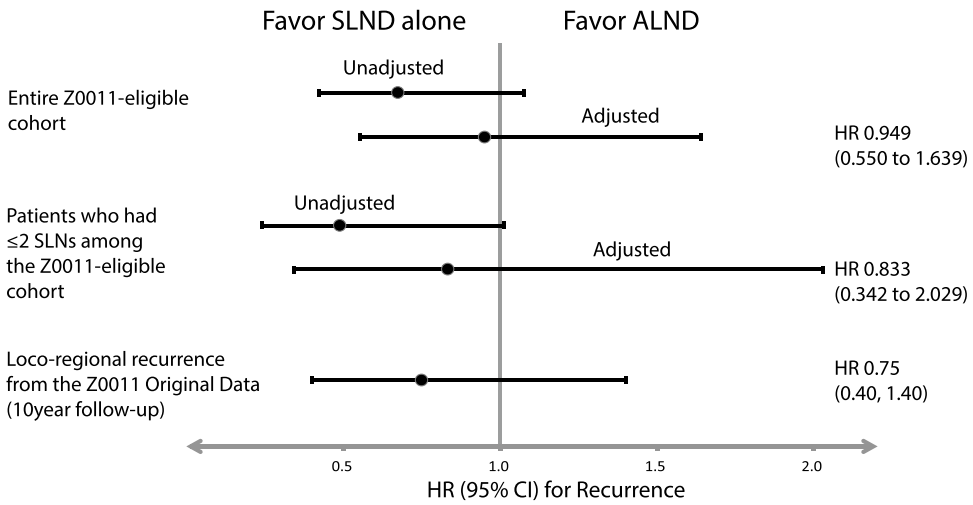

Fig. 2 Adjusted hazard ratios of omitting conventional axillary dissection, for disease recurrence after propensity score matching *ALND* axillary lymph node dissection, *CI* confidence interval, *HR* hazard ratio, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection, *OS* overall survival

excluded from the present study. However, the vast majority of patients who fulfilled the Z0011 criteria had a low burden of node metastasis, regardless of whether the metastatic LNs were detected via SLND or image-guided cytology. Wellington et al. [18] have also reported that the use of axillary sonography is unlikely to change the proportion of ALND, despite the possible administration of neoadjuvant chemotherapy. Moreover, the proportion of patients with suspicious axillary findings did not differ between our study groups (Table 1). The possible exclusion of patients who had suspicious axillary findings is unlikely to be biased and would likely have minimal effect on our findings.

It is recommended that >10 LNs be acquired during conventional ALND to achieve an adequate axillary assessment during breast cancer staging. Similarly, the number of acquired SLNs during SLND is thought to influence the predictive quality and accuracy [19]. The reported false-negative rate of SLND is 6.7% with ≥ 3 SLNs, although this rate increases to 9.7% for 2 SLNs and 13.0% for 1 SLN [20], and SLND only removes an average of 2 LNs in most studies [21–23]. Interestingly, although surgeons might be biased toward the removal of additional SLNs for Z0011-eligible patients, the median number of SLNs has not changed the between pre- and post-Z0011 eras [24, 25]. To adequately apply the Z0011 strategy and improve the accuracy of SLND, surgeons may aim to harvest more SLNs. However, only ≤ 2 SLNs can be obtained in a considerable proportion of patients (e.g., 55% in our cohort). Thus, the applicability of the Z0011 results within this patient subgroup is a clinically significant issue, based on the relatively poor accuracy of SLND, that should be validated separately.

Our findings demonstrated that a small number of SLNs had a minimal impact on recurrence after Z0011-based treatment. This result may reflect the excellent outcomes among patients who fulfilled the Z0011 criteria. Furthermore, the present study included a higher proportion of patients who underwent adjuvant systemic therapies than the Z0011 study (87% vs. 58%), as well as a higher proportion of endocrine therapy for ER-positive cases (almost 100% vs. 79%). It is possible that the lower number of recurrences in the present study could be attributed to the higher proportion of adjuvant systemic therapy, although it may also be related to the ordinal position of the first positive LN among all removed SLNs. For example, Yi et al. [19] demonstrated that the "hottest" SLN during SLND was the first positive LN in 69% of the 777 patients with positive SLNs, and that the likelihood of metastatic disease decreased with each successive SLN, to the point that the first positive SLN was at the third or greater SLN in only 9% of cases with ≥ 3 LNs removed. In this context, the SLN is defined as the first LN in a regional lymphatic basin to accept drainage from the primary tumor [26–28], which suggests that latter SLNs are less likely to provide predictive value relative to the first one.

The present study's retrospective design raises the possibility of biases disguising poorer outcomes in the SLND alone group than in the ALND group. Furthermore, the inter-group differences suggested a possibility of selection bias affecting the decision to omit ALND (Table 1). Thus, to reduce those possible biases, we performed PS matching and re-evaluated the outcomes, although this failed to reveal a significant difference in recurrence in the PS-matched analyses. As the Z0011 trial results have been confirmed using long-term follow-up data and several validation studies, it appears reasonable to use a retrospective cohort study in place of a randomized controlled trial, and the use of PS matching is a useful approach to overcoming the inherent limitations of the retrospective design.

We selected disease recurrence as the present study's end-point, based on a median follow-up of 4 years and an 8-year interval from the Z0011 report. This is because our relatively short follow-up period is likely insufficient to identify a significant difference in mortalities, especially given

the patients' excellent prognosis and the fact that we only detected 28 deaths (Table 1). We also detected fewer LRR events than in the Z0011 study, which makes this outcome inappropriate as a study end-point. Furthermore, distant recurrence frequently leads to death in most cases, and was more common than LRR (66 events vs. 29 events), which is why we combined both distance recurrences and LRRs as the study end-point. This approach is less ideal than evaluating DFS or OS as an end-point, although it is a better surrogate for survival than LRR alone. Moreover, evaluating disease recurrence among patients with early breast cancer remains clinically relevant (apart from survival analyses), as breast cancer-related mortality typically occurs later than recurrence.

The present study revealed median follow-up periods of 56 months in the ALND group and 40 months in the SLND alone group, which are relatively short given that Z0011-eligible patients have early-stage disease and typically ER-positive tumors. This is important, as patients with ER-positive breast cancer have a long-term risk of disease recurrence [29, 30], and prolonged follow-up is needed to determine whether there is a significant difference in late recurrence between the ALND and SLND alone groups. Nevertheless, additional follow-up from years 5 to 10 did not change the major findings of the Z0011 trial, despite most of the participants having ER-positive tumors. Furthermore, between years 5 and 10, only 11 additional LRRs were detected in the Z0011 cohort [3, 4], and the incremental decreases in DFS between years 5 and 10 (−3.7% for the SLND alone group and −4.0% for the ALND group) were not meaningfully different [1, 2]. Thus, based on the minimal changes during long-term follow-up of the Z0011 cohort, we do not believe that our findings are likely to change based on a prolonged follow-up interval.

In conclusion, this retrospective cohort study of 1750 Z0011-eligible Asian patients with breast cancer revealed that ALND could be omitted without increasing the risk of disease recurrence after a median follow-up of 50 months. This result was confirmed in PS-matched analyses to minimize the potential for selection biases. Furthermore, among patients with ≤2 SLNs removed, disease recurrence was not significantly different between the SLND alone group and the ALND group. These results suggest that the small number of SLNs had minimal impact on the risk of disease recurrence based on the approach of the ACOSOG Z0011 trial.

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Compliance with ethical standards

Conflict of interest The authors declare that no actual or potential conflict of interest exists.

Ethical approval All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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