Research Square

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Impact of the ACOSOG Z0011 Trial on Surgical Practice in Asian Patients: Comparison of Trends in Axillary Surgery for Breast Cancer Between Korean and Dutch Cohorts

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Research Article

Keywords: Breast cancer, axillary lymph node dissection, sentinel lymph node biopsy, time-trend analysis, the ACOSOG-Z0011 trial

Posted Date: July 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-629894/v1

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Abstract

Purpose

Since the publication of the Z0011 trial, practice-changing clinical guidelines for breast surgery have been developed. Although recent studies confirmed the feasibility of the Z0011 strategy in Asian populations, there has been no study on the trends of axillary surgery in Asian cohort. This study aimed to investigate the time trend of axillary surgery for breast cancer in Korea and compare it with that in Dutch cohort to understand the impact of the Z0011 trial.

Methods

We collected prospectively constructed data from the nationwide Korean Breast Cancer Registry (KBCR). We identified patients who underwent sentinel node biopsy followed by breast-conserving surgery from 2011 to 2018 and were found to have pathological stage T1-2N1-3M0 disease. Regression analyses were performed to compare the downward trend of axillary lymph node dissection (ALND) in our cohort with that previously reported in a Dutch cohort.

Results

From KBCR data, 7,478 patients met the inclusion criteria. The proportion of ALND significantly decreased from 2011 (76.6%) to 2018 (47.5%). Multivariate analysis revealed that earlier year at diagnosis, larger tumor size, and lymphatic invasion were associated with a higher odds ratio of performing ALND. Compared to Dutch cohort, the downward trend of ALND in Korea was significantly more gradual (annual percent change: 30.1% *vs.* 5.8%, $P < 0.001$).

Conclusions

This study demonstrated a downward trend of ALND in Korean patients with breast cancer. However, the rate of decrease was significantly slower than that in Dutch cohort, indicating the need to spread the Z0011 strategy in Asia.

Introduction

The surgical approach to the axilla in patients with breast cancer has changed dramatically over the past two decades [1]. Results of recent randomized control trials have provided practice-changing recommendations for indications of axillary lymph node dissection (ALND) [2–5]. According to the American College of Surgeons Oncology Group Z0011 trial, patients who meet all the Z0011 selection criteria (cT1-2N0 disease with 1–2 positive sentinel nodes treated with breast-conserving surgery [BCS] followed by whole breast radiotherapy) do not need further axillary surgery [6, 7]. Clinical practice recommendations such as the National Comprehensive Cancer Network guidelines and the American Society of Clinical Oncology guidelines were then modified to omit ALND for these patients [8, 9]. However, there have been wide variations in axillary management of patients with breast cancer among

Western countries [10, 11], which may be partly because some physicians may not be aware of or familiar with the recommendations, or because they are reluctant to adhere to the guidelines. Indeed, some researchers have argued that the results of the Z0011 trial should be considered unreliable due to incomplete patient accrual and selection of a favorable subgroup consisting of postmenopausal women with small tumors [12–15]. Thus, it would be necessary to validate the Z0011 results in a larger cohort of patients with various conditions and then to modify, if necessary, and spread unified clinical guidelines to allow for evidence-based practices [10, 11].

There is similar uncertainty regarding appropriate adoption of current surgical strategies, which have been established in Western countries, in Asian patients as breast cancers in Asian women have several characteristics different from those in Western women [16]. For example, it has been reported that there are higher proportions of premenopausal patients and basal-like breast cancers in Asia than in Western countries [17, 18]. Therefore, while a few recent studies have demonstrated the feasibility of the Z0011 strategy in the Asian population, further validation studies would certainly benefit patients with breast cancer as well as breast surgeons in Asia [19, 20]. Meanwhile, there has been no study on the trends of axillary surgery in a large Asian cohort, and it is unclear whether or not surgeons in Asia have been slower to adopt the results of the Z0011 trial than those in Europe. Therefore, we aimed to analyze the trends of axillary surgery for breast cancer in a large Korean cohort and compare the decreasing trends of ALND with those in Europe to assess the impact of the Z0011 trial over a period of time.

Patients And Methods

Korean Breast Cancer Registry (KBCR)

The KBCR is a web-based, prospectively maintained nationwide database managed by the Korean Breast Cancer Society. Since 1997, 102 institutions have participated in this registry. From the initial construction of the KBCR database, principal investigators from every institution have agreed on the principles and processes of utilizing this database for research. Essential registry items include patients' unique national identification number, sex, age, type of surgery, and cancer stage according to the 7th edition of the American Joint Committee on Cancer classification. Moreover, data on biological characteristics (such as estrogen receptor [ER], human epidermal growth factor receptor 2 [HER2] status) and adjuvant treatment (such as radiotherapy, chemotherapy, and hormonal therapy) are collected. According to the guidelines of utilizing the KBCR database, this study was approved by the Institutional Review Board (IRB) of Hanyang University Hospital. The Korean Breast Cancer Society approved our research objective and our request to access data from July 2020.

Since information on the clinical stage was not available from the KBCR, we selected patients who would best meet the Z0011 criteria as follows. We identified patients who underwent sentinel lymph node biopsy (SLNB) as SLNB is performed in patients with cT1-2 N0 M0 disease. Of them, patients with pathological stage T1-2 N1-3 M0 disease who underwent BCS were finally selected (Fig. 1).

Data on the following variables were collected: age, year of surgery, histology, pathologic N stage, tumor grade, hormone receptor status, HER2 status, lymphatic invasion, number of nodes examined, number of positive nodes, and year-wise frequency of ALND from 2011 to 2018.

Dutch population-based study: European cohort

The Dutch study population was described in detail in a previous study [21]. Briefly, data were obtained from their multidisciplinary nationwide registry of all diagnostic and treatment modalities performed in patients who had undergone surgical treatment for breast cancer from January 2011 to October 2015. Their study sample included 8,191 patients diagnosed with cT1-2 N0 M0 invasive breast cancer and 1–2 positive sentinel lymph nodes. A positive sentinel node included micrometastases and macrometastases. Patients aged < 18 years, those who had received neoadjuvant systemic therapy, those with a prior history of breast surgery, and those whose data on axillary surgery was incomplete were excluded. Data from 85 Dutch hospitals were included in this study. We extracted the year-wise number and proportion of patients who underwent ALND between 2011 and 2015 from the published article and compared the downward trends of ALND in their population with those in our population.

Study endpoints

The outcome of interest was trends in surgical management of the axilla. Patients were divided into two groups based on the type of axillary surgery as follows: SLNB alone or SLNB + ALND. The primary endpoint was the year-wise percentage of patients who underwent ALND in Korean cohort between 2011 and 2018. The secondary endpoint was the difference in trends of axillary surgery between Korean and Dutch cohorts. In addition, we identified clinicopathological factors associated with the type of axillary surgery performed in Korean cohort.

Statistical analyses

Descriptive analyses were used to analyze the trends in axillary surgery. Data are presented as frequencies and percentages (%) for categorical variables. Univariate associations between variables were examined using the chi-square test. Univariate and multivariate logistic regression analyses were performed to investigate the probability of performing ALND. Joinpoint regression analyses were used to compare the annual percent change (APC) of patients undergoing ALND between Korean and Dutch cohorts from 2011 to 2015. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). JOINPOINT Version 4.8.0.1 (Statistical Research and Applications Branch, National Cancer Institute) was used to fit the joinpoint regression model with an annual grid search.

Results

Characteristics of the Korean cohort

The clinicopathological characteristics of the 7,478 Korean patients with T1-2 N1-3 M0 disease who had not received neoadjuvant chemotherapy and underwent BCS and SLNB from 2011 to 2018 are demonstrated in Table 1. The mean age was 51 years (range, 16–90 years), with 767 (10.3%) patients aged < 40 years and 2,755 (36.8%) patients aged 40–49 years. Further, 44.4% of patients had pT2 lesions, with 487 (6.5%) patients having multifocal tumors. The histologic subtype was invasive ductal carcinoma (IDC) in 6,232 (83.3%) cases. Approximately 60%) of patients had tumors with low histologic grade (I or II), and 2,811 (37.6%) patients had lymphatic invasion. ER-positive tumors were observed in 5,534 (74.0%) cases, and HER2 overexpression was confirmed in 1,047 (14.0%) cases.

Table 1
Clinicopathological characteristics of 7,478 Korean patients who met the Z0011 criteria

	Total number (n = 7,478)	SLNB + ALND (n = 4,834)	SLNB alone (n = 2,644)	P value[a]
Age at surgery (years)				**0.738**
< 40	767	486 (63.4%)	281 (36.6%)	
40–49	2,755	1,790 (65.0)	965 (35.0)	
50–59	2,482	1,612 (64.9)	870 (35.1)	
60–69	1,060	690 (65.1)	370 (34.9)	
70–79	360	227 (63.1)	133 (36.9)	
> 80	48	27 (56.3)	21 (43.7)	
Unknown	6			
Year of surgery				**< 0.0001**
2011	1,113	853 (76.6)	260 (23.4)	
2012	1,252	909 (72.6)	343 (27.4)	
2013	1,278	891 (69.7)	387 (30.3)	
2014	1,241	784 (63.2)	457 (36.8)	
2015	801	487 (60.8)	314 (39.2)	
2016	727	394 (54.2)	333 (45.8)	
2017	784	382 (48.7)	402 (51.3)	
2018	282	134 (47.5)	148 (52.5)	
pT				**< 0.0001**
pT1	4,156	2,490 (58.5)	1,666 (41.5)	
pT2	3,322	2,344 (70.6)	978 (29.4)	
Multifocality				**0.094**
Single lesion	5,362	3,407 (63.5)	1,955 (36.5)	
Multifocal lesion	487	328 (67.4)	159 (32.6)	

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; pT, pathologic tumor stage; IDC, invasive ductal carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

[a] Univariable chi-square test

	Total number (n = 7,478)	SLNB + ALND (n = 4,834)	SLNB alone (n = 2,644)	P value[a]
Unknown	1,629			
Histologic subtype				**0.013**
IDC	6,232	4,067 (65.3)	2,165 (34.7)	
Other	1,246	767 (61.6)	479 (38.4)	
Histologic grade				**< 0.0001**
	915	600 (65.6)	315 (34.4)	
	3,605	2,235 (62.0)	1,370 (38.0)	
	2,085	1,442 (69.2)	643 (30.8)	
Unknown	873			
Lymphatic invasion				**< 0.0001**
No	2,899	1,731 (59.7)	1,168 (40.3)	
Yes	2,811	1,958 (69.7)	853 (30.3)	
Unknown	1,768			
ER status				**< 0.0001**
Negative	1,212	843 (69.6)	369 (30.4)	
Positive	5,534	3,516 (63.5)	2,018 (36.5)	
Unknown	732			
HER2 status				**< 0.001**
Negative	5,180	3,299 (63.7)	1,881 (36.3)	
Positive	1,047	728 (69.5)	319 (30.5)	
Unknown	1,251			

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; pT, pathologic tumor stage; IDC, invasive ductal carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

[a] Univariable chi-square test

Characteristics of the SLNB + ALND group in the Korean cohort

The proportion of ALND gradually decreased from 2011 (76.6%) to 2018 (47.5%) ($P < 0.001$; Fig. 2). Joinpoint regression analysis indicated a significant reduction of 5.8% per year from 2011 to 2015 ($P < 0.001$). A multivariate model adjusted for age at surgery, year of surgery, pathologic tumor stage, multifocality, histologic subtype, histologic grade, lymphatic invasion, ER status, and HER2 status revealed that earlier year of surgery, larger tumor size, and lymphatic invasion ($P < 0.001$) were factors associated with a higher odds ratio of performing ALND (Table 2).

Table 2
Univariate and multivariate analyses for the performance of axillary lymph node dissection in 7,478 Korean patients who met the Z0011 criteria

Variables	Univariate Analysis			Multivariate Analysis [a]		
	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Age at surgery						
< 40	Ref.					
40–49	1.072	0.908–1.267	0.410			
50–59	1.071	0.905–1.268	0.423			
60–69	1.078	0.888–1.309	0.446			
70–79	0.987	0.761–1.279	0.920			
> 80	0.743	0.413–1.340	0.324			
Year of surgery						
2011	Ref.			Ref.		
2012	0.808	0.670–0.973	0.025	0.831	0.664–1.039	0.104
2013	0.702	0.584–0.843	< 0.0001	0.710	0.566–0.891	0.003
2014	0.523	0.437–0.626	< 0.0001	0.494	0.394–0.619	< 0.0001
2015	0.473	0.388–0.577	< 0.0001	0.381	0.301–0.482	< 0.0001
2016	0.361	0.295–0.441	< 0.0001	0.294	0.231–0.373	< 0.0001
2017	0.290	0.238–0.353	< 0.0001	0.277	0.216–0.354	< 0.0001
2018	0.276	0.210–0.362	< 0.0001	0.309	0.224–0.427	< 0.0001

pT, pathologic tumor stage; IDC, invasive ductal carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; CI, confidence interval

[a]Adjusted for age at surgery, year of surgery, pathologic tumor stage, multifocality, histologic subtype, histologic grade, lymphatic invasion, ER status, and HER2 status

Variables	Univariate Analysis			Multivariate Analysis [a]		
	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
pT						
pT1	Ref.			Ref.		
pT2	1.604	1.455–1.767	< 0.0001	1.513	1.339–1.710	< 0.0001
Multifocality						
Single lesion	Ref.					
Multifocal lesion	1.184	0.972–1.442	0.094			
Histologic subtype						
IDC	1.173	1.035–1.330	0.013	1.177	0.907–1.528	0.220
Others	Ref.			Ref.		
Histologic grade						
	Ref.			Ref.		
	0.856	0.736–0.997	0.046	0.785	0.656–0.940	0.009
	1.177	0.998–1.389	0.053	0.939	0.759–1.162	0.564
Lymphatic invasion						
No	Ref.			Ref.		
Yes	1.549	1.388–1.728	< 0.0001	1.572	1.393–1.773	< 0.0001
ER status						
Negative	Ref.			Ref.		
Positive	0.763	0.667–0.872	< 0.0001	0.852	0.713–1.018	0.077

pT, pathologic tumor stage; IDC, invasive ductal carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; CI, confidence interval

[a]Adjusted for age at surgery, year of surgery, pathologic tumor stage, multifocality, histologic subtype, histologic grade, lymphatic invasion, ER status, and HER2 status

Variables	Univariate Analysis			Multivariate Analysis [a]		
	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
HER2 status						
Negative	Ref.			Ref.		
Positive	1.301	1.128–1.502	< 0.0001	1.188	1.004–1.406	0.044

pT, pathologic tumor stage; IDC, invasive ductal carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; CI, confidence interval

[a]Adjusted for age at surgery, year of surgery, pathologic tumor stage, multifocality, histologic subtype, histologic grade, lymphatic invasion, ER status, and HER2 status

Comparison of trends on ALND between Korean and Dutch cohorts

From 2011 to 2015, the downward trend of ALND in the Korean cohort was significantly more gradual than that in the Dutch cohort (APC 5.8% *vs*. 30.1%, P < 0.001, Fig. 3). Although 75% of Dutch patients and 77% of Korean patients underwent ALND in 2011, 17% Dutch patients and 61% Korean patients underwent ALND in 2015 (Fig. 3).

Discussion

Several characteristics, including tumor biology and demographics, vary between Asian and Western patients with breast cancer [17, 18]. Racial differences could affect the adoption of current surgical strategies established in Western countries. Although our study, based on a large Korean nationwide database, revealed downward trends of ALND in our breast cancer patients who met the Z0011 criteria, the downward trend was significantly more gradual than that in the Dutch cohort. To the best of our knowledge, this is the first study to report the downward trend of axillary surgery in Asian patients with breast cancer and to compare the degrees of the downward trend of axillary surgery between Asian and Western countries.

Compared to the Z0011 participants, those in our study had larger tumor size, more frequent lymphatic invasion, and younger age. In the Z0011 cohort, approximately 30% of patients had T2 lesions, 28% of patients had lymphatic invasion, and 25% of patients were < 50 years old [6]. In contrast, in our study cohort, approximately 45% of patients had T2 lesions, 49% of patients had lymphatic invasion, and 47% of patients were < 50 years old. In the Dutch cohort, 37% of patients had T2 lesions, no information on lymphatic invasion was reported, and only 20% of patients were < 50 years old, similar to the Z0011 cohort [21]. A recent Japanese study by Kittaka et al. evaluated Japanese patients who met the Z0011 criteria and reported that their patients had larger tumors and more frequent lymphatic invasion than the

Z0011 participants [22], which is consistent with our study findings. These differences in tumor biology and demographic characteristics between the Asian and Z0011 cohorts might underlie the difference in the trend of the surgical management of the axilla. We speculate that more unfavorable tumor characteristics in Asian women might be the reason why surgeons in Asia are less willing to omit ALND even in some patients who meet the Z0011 criteria. Our multivariate analysis revealed that larger tumor size and lymphatic invasion were associated with a higher odds ratio of performing ALND, indicating that surgeons preferred to perform completion ALND over SLNB alone in such cases.

Consistent with our findings, Liu et al. reported that many surgeons in China preferred to perform completion ALND even in patients who met the Z0011 criteria [19]. Although Chinese surgeons were aware of the Z0011 trial results, 42% of them still performed ALND in most cases considering that clinical situations in many areas of China were different from those in Western countries. For example, many patients do not receive standard adjuvant treatment following surgery in suburban areas of China due to patient intention, financial issues, and medical conditions. Thus, some Chinese surgeons have argued that the Z0011 trial results may not be applicable in the clinical setting in China and that they prefer to choose radical surgery for any number of positive sentinel lymph nodes. In addition, some Chinese surgeons were uncertain whether the Western trial results could be applicable to the Chinese population due to differences in clinical characteristics between Asian and Western patients. Furthermore, there have been some debates on the potential selection bias related to the enrollment of patients in the Z0011 trial. Patients with a good prognosis alone were enrolled, and the trial was closed early with < 50% target accrual [23, 24]. The aforementioned explanations may also explain the downward trend of ALND in the Korean cohort that is not as fast as that in the Dutch cohort.

Several recent studies in large Asian cohorts have validated that the Z0011 strategy could be safely applied to Asian patients. Jung et al. reported that ALND omission in the Asian cohort did not increase the risk of disease recurrence during a median follow-up period of 50 months [20]. A prospective single-arm study by Kittaka et al. showed that the 5-year cumulative rate of locoregional recurrences was only 1.3% in patients undergoing BCS with SLNB alone followed by radiotherapy [22]. Although prolonged follow-up is needed to determine the oncologic safety with regard to late recurrences, it might be feasible to apply the Z0011 strategy in Asian patients. Taken together, despite of differences in tumor biology and demographics along with clinical situations in Asian countries, more efforts are needed to spread the Z0011 strategy.

Previous studies have reported several factors associated with performing ALND in early breast cancer. According to recently published data from the European Society of Breast Cancer Specialists, the factors associated with a higher odds ratio of performing ALND in patients meeting the Z0011 criteria were earlier year of surgery, younger age, larger tumor size, and a higher tumor grade [11]. In a Dutch population-based study, younger patients with invasive lobular subtype, those with a higher tumor grade, and those treated in a general non-teaching hospital underwent completion ALND more frequently. Our results similarly demonstrated that patients with poor prognostic tumor biology, such as large size and lymphatic invasion, underwent ALND more frequently than other patients. With regard to surgeons'

preferences, a survey study by Morrow et al. reported that surgeons in higher patient volume centers and those participating in a multidisciplinary tumor board had a lower propensity for performing ALND, suggesting the need for education targeting breast surgeons working in lower-volume centers [25].

Our study is limited by its retrospective design and lack of data on the clinical T and N stages. Instead, we postulated that patients with T1-2 N1-3 M0 disease who had undergone SLNB and BCS would best meet the Z0011 criteria. Despite these limitations, our study has a strength in analyzing population-based nationwide data, including diverse surgeons' preferences. To our knowledge, this is the first study reporting real-world data on trends of axillary surgery in Asian patients with breast cancer.

In summary, our study demonstrated a downward trend of ALND in Korea patients with breast cancer who met the Z0011 criteria. However, the rate of decrease was significantly slower than that in Dutch cohort, indicating the need to spread the Z0011 strategy in Asia.

Declarations

FUNDING SOURCE

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURES

All authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to thank the Department of Biostatistics, Hanyang University College of Medicine, for assistance with statistical analysis. This study was supported by the Korean Breast Cancer Society.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

AUTHORS CONTRIBUTION

Dr. Min Sung Chung had full access to all the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chihwan Cha, Min Sung Chung

Data collection: Korean Breast Cancer Society

Data analysis: Chihwan Cha, Nayeon Choi, Hanpyo Hong

Drafting of the manuscript: Chihwan Cha

Revision of the manuscript for important intellectual content: All authors.

Study supervision: Min Sung Chung

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Figures

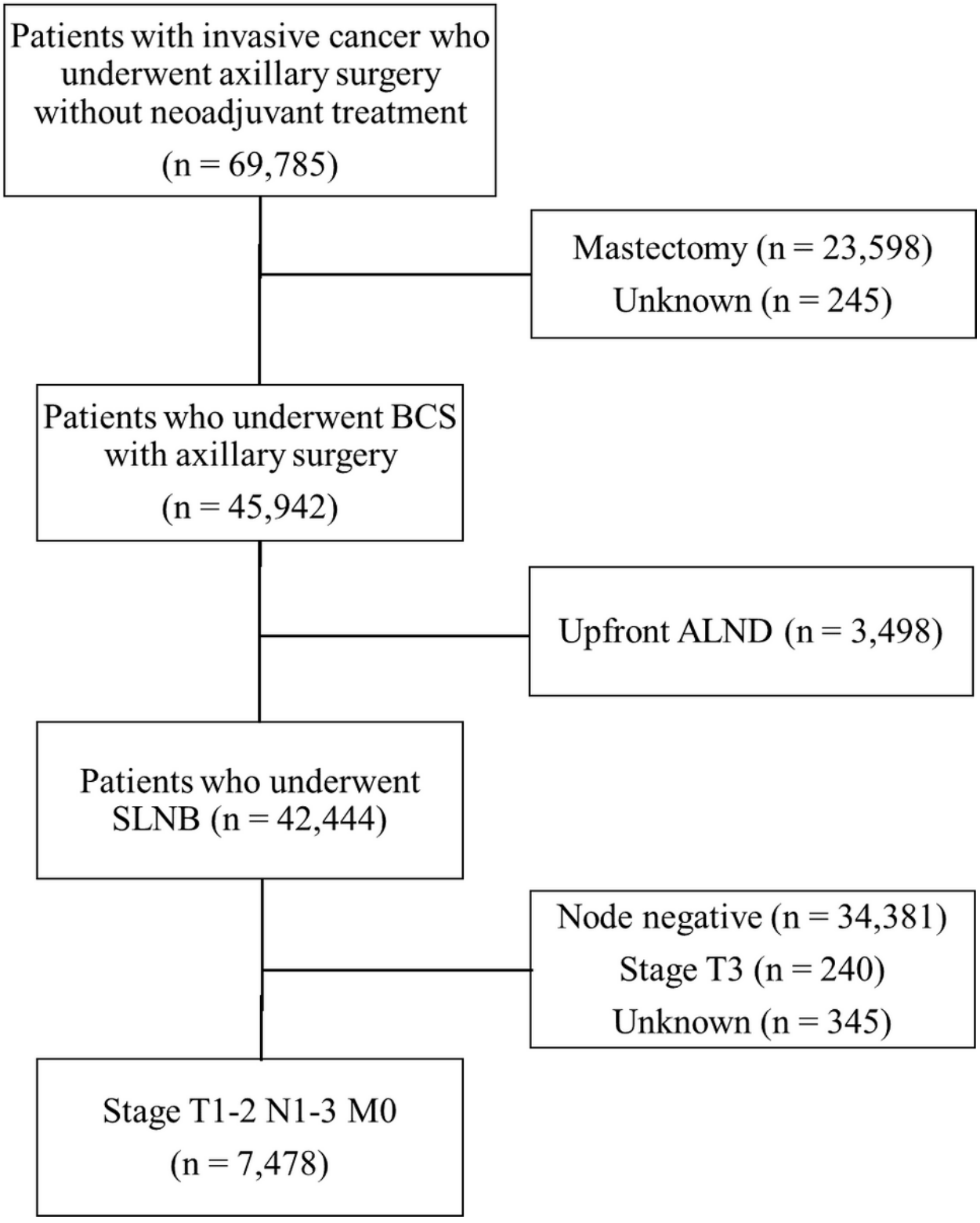

Figure 1

CONSORT diagram of the study population BCS, breast-conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

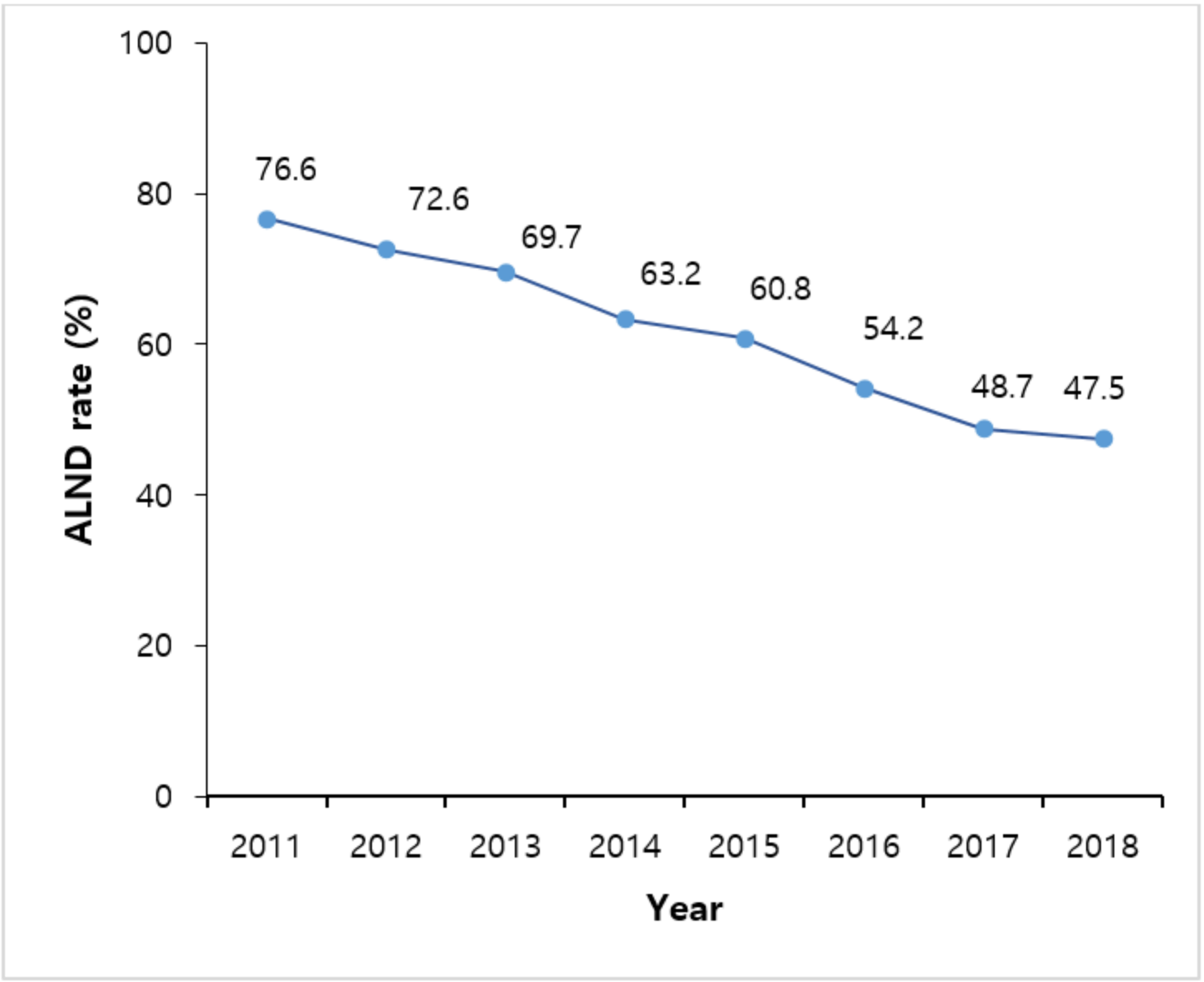

Figure 2

Rates of axillary lymph node dissection from 2011 to 2018 in 7,478 Korean patients who met the Z0011 criteria

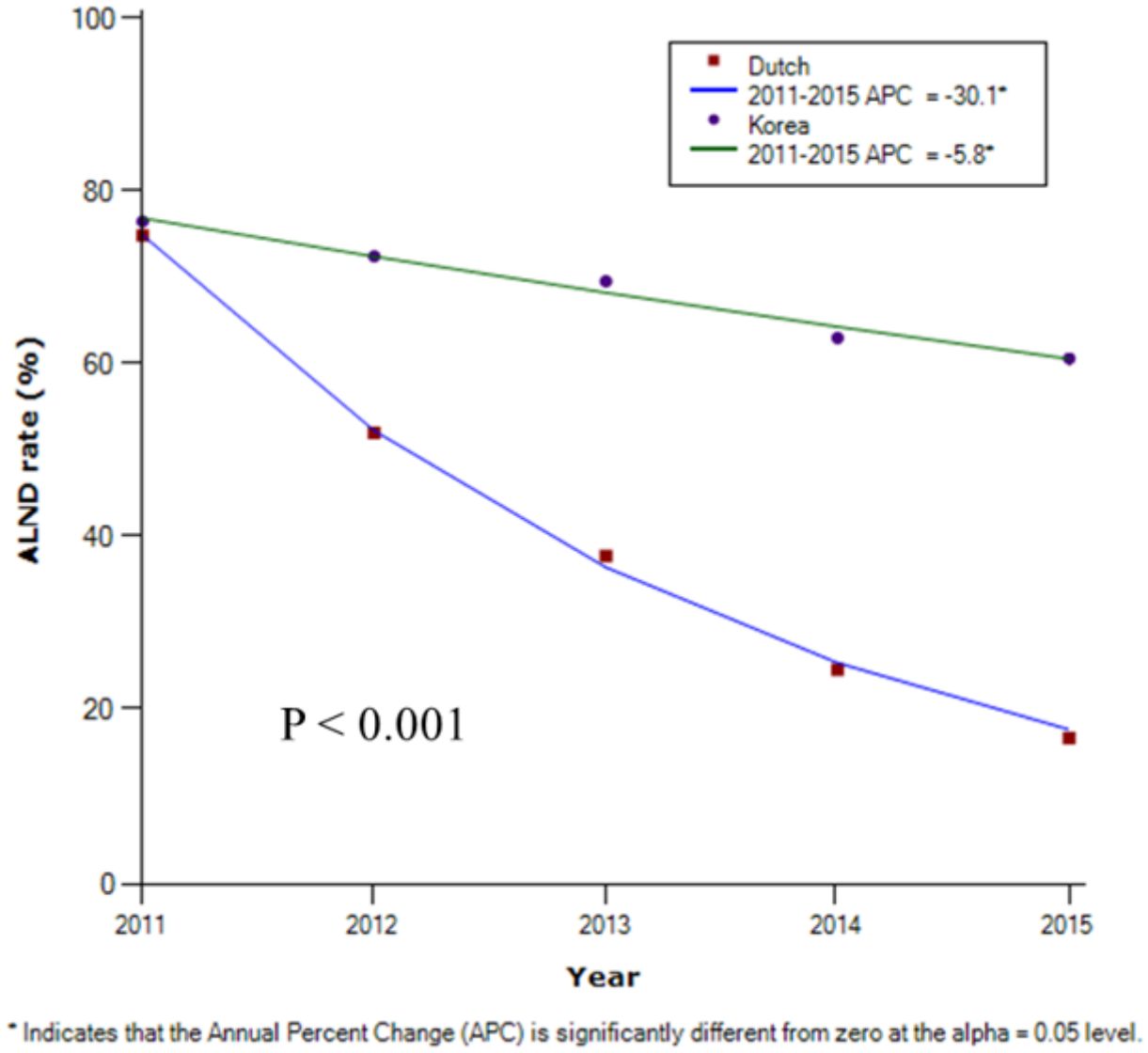

Figure 3

Downward trends of axillary lymph node dissection in the Korean and Dutch cohorts from 2011 to 2015
ALND, axillary lymph node dissection; APC, annual percent change